

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

THIS PAGE BLANK (USPTO)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 September 2002 (26.09.2002)

PCT

(10) International Publication Number
WO 02/074312 A1

(51) International Patent Classification⁷: **A61K 31/505**,
C07D 487/04, A61P 3/00, 15/00, 25/00 // (C07D 487/04,
239:00, 231:00)

Pfizer Central Research and Development, Ramsgate Road,
Sandwich, Kent CT13 9NJ (GB).

(21) International Application Number: PCT/IB02/00679

(74) Agents: **WOOD, David, J.** et al.; Pfizer Limited, Rams-
gate Road, Sandwich, Kent CT13 9NJ (GB).

(22) International Filing Date: 7 March 2002 (07.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0106651.3 16 March 2001 (16.03.2001) GB
0106561.4 16 March 2001 (16.03.2001) GB

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZM, ZW.

(71) Applicant (*for GB only*): **PFIZER LIMITED** [GB/GB];
Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

(71) Applicant (*for all designated States except GB*): **PFIZER
INC.** [US/US]; 235 East 42nd Street, New York, NY 10017
(US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **ALLERTON, Char-
lotte, Moira, Norfor** [GB/GB]; Pfizer Global Research and
Development, Ramsgate Road, Sandwich, Kent CT13 9NJ
(GB). **BARBER, Christopher, Gordon** [GB/GB]; Pfizer
Global Research and Development, Ramsgate Road, Sand-
wich, Kent CT13 9NJ (GB). **KEMP, Mark, Ian** [GB/GB];

Published:

— with international search report

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: PYRAZOLO'4,3-D.PYRIMIDINONE COMPOUNDS AS CGMP PDE INHIBITORS

(57) Abstract: Compounds of general formula (I), or pharmaceutically or veterinarily acceptable salts, solvates, polymorphs or pro-drugs thereof wherein: wherein R¹, R², R³, R⁴, X and A have the meanings given herein which are useful in the curative and prophylactic treatment of a medical condition for which inhibition of a cyclic guanosine 3',5'-monophosphate phosphodiesterase (e.g. cGMP PDE5) is desired.



WO 02/074312 A1

PYRAZOLO[4,3-d]PYRIMIDINONE COMPOUNDS AS CGMP PDE INHIBITORS

Field of the Invention

5

This invention relates to pharmaceutically useful compounds, in particular compounds which are useful in the inhibition of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs), such as type 5 cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDE5). The compounds therefore have utility in a variety of therapeutic areas, including male
10 erectile dysfunction (MED).

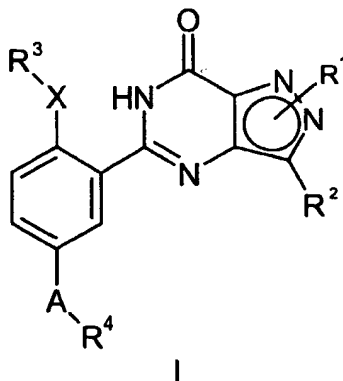
International patent application WO 01/27112 discloses the use of certain pyrazolo[4,3-d]pyrimidinone compounds in the treatment of a variety of
15 conditions and in particular MED.

The present application provides further pyrazolo[4,3-d]pyrimidinone compounds.

Disclosure of the Invention

20

According to the present invention, there are provided compounds of general formula I:



25 or pharmaceutically or veterinarily acceptable salts, solvates, polymorphs or pro-drugs thereof wherein:

A represents C(O) or CH(OH);

X represents O or NR⁵;

- 5 R¹, R³, R⁴ and R⁵ independently represent H, C₁-C₆ alkyl, Het, C₁-C₆ alkylHet, aryl or C₁-C₆ alkylaryl (which latter five groups may all be optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR⁶, OC(O)R⁶, C(O)R⁶, C(O)OR⁶, NR⁶C(O)NR⁷R⁸, NR⁶C(O)OR⁶, OC(O)NR⁷R⁸, C(O)NR⁹R¹⁰, NR⁹R¹⁰, SO₂NR⁹R¹⁰, SO₂R¹¹, C₁-C₆ alkyl, Het, C₁-C₆ alkylHet, aryl
10 or C₁-C₆ alkylaryl wherein said latter five substituent and/or terminal groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR¹², OC(O)R¹², C(O)R¹², C(O)OR¹², NR¹²C(O)NR¹³R¹⁴, NR¹²C(O)OR¹², OC(O)NR¹³R¹⁴, C(O)NR¹⁵R¹⁶, NR¹⁵R¹⁶, SO₂NR¹⁵R¹⁶, SO₂R¹⁷); or when X represents NR⁵ then R³ and R⁵ together with
15 the nitrogen atom to which they are bound can form a heterocyclic ring which is optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR¹², OC(O)R¹², C(O)R¹², C(O)OR¹², NR¹²C(O)NR¹³R¹⁴, NR¹²C(O)OR¹², OC(O)NR¹³R¹⁴, C(O)NR¹⁵R¹⁶, NR¹⁵R¹⁶, SO₂NR¹⁵R¹⁶, SO₂R¹⁷;
- 20 R² represents H, halo, cyano, nitro, OR⁶, OC(O)R⁶, C(O)R⁶, C(O)OR⁶, NR⁶C(O)NR⁷R⁸, NR⁶C(O)OR⁶, OC(O)NR⁷R⁸, C(O)NR⁹R¹⁰, NR⁹R¹⁰, SO₂NR⁹R¹⁰, SO₂R¹¹, C₁-C₆ alkyl, Het, C₁-C₆ alkylHet, aryl or C₁-C₆ alkylaryl (which latter five groups may all be optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR⁶, OC(O)R⁶, C(O)R⁶, C(O)OR⁶,
25 NR⁶C(O)NR⁷R⁸, NR⁶C(O)OR⁶, OC(O)NR⁷R⁸, C(O)NR⁹R¹⁰, NR⁹R¹⁰, SO₂NR⁹R¹⁰, SO₂R¹¹, C₁-C₆ alkyl, Het, C₁-C₆ alkylHet, aryl or C₁-C₆ alkylaryl wherein said latter five substituent and/or terminal groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR¹², OC(O)R¹², C(O)R¹², C(O)OR¹², NR¹²C(O)NR¹³R¹⁴, NR¹²C(O)OR¹², OC(O)NR¹³R¹⁴, C(O)NR¹⁵R¹⁶, NR¹⁵R¹⁶, SO₂NR¹⁵R¹⁶, SO₂R¹⁷);
30

R⁶ represents H, C₁-C₆ alkyl, Het, C₁-C₆ alkylHet, aryl or C₁-C₆ alkylaryl (which latter five groups are all optionally substituted and/or terminated with one or more

substituents selected from halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17} ;

- 5 R^7 and R^8 independently represent H, C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl (which latter five groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17}); or R^7 and R^8
 10 together with the nitrogen atom to which they are bound can form a heterocyclic ring;

- R^9 and R^{10} independently represent H, $C(O)R^6$, SO_2R^{11} , C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl (which latter five groups are all optionally
 15 substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17}); or R^9 and R^{10} together with the nitrogen atom to which they are bound can form a heterocyclic ring;

20

- wherein when R^7 and R^8 , or R^9 and R^{10} together with the nitrogen atom to which they are bound form a heterocyclic ring, said heterocyclic ring is optionally substituted and/or terminated with one or more substituents selected from: halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$,
 25 $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17} ;

- R^{11} represents a C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl group is optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$,
 30 $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17} ;

R^{12} represents H or C_1 - C_6 alkyl;

R^{13} and R^{14} independently represent H or C_1 - C_6 alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are bound can form a heterocyclic ring;

R^{15} and R^{16} independently represent H, $C(O)R^{12}$, SO_2R^{17} or C_1 - C_6 alkyl; or R^{15} and R^{16} together with the nitrogen atom to which they are bound can form a heterocyclic ring;

R^{17} represents C_1 - C_6 alkyl;

10 Het represents an optionally substituted four- to twelve-membered heterocyclic group, which group contains one or more heteroatoms selected from nitrogen, oxygen, sulphur and mixtures thereof;

with the proviso that when X represents O and R^1 represents H, C_1 - C_3 alkyl optionally substituted with fluoro or C_3 - C_5 cycloalkyl then

R^2 does not represent H, C_1 - C_6 alkyl optionally substituted with one or more fluoro substituents or with C_3 - C_6 cycloalkyl; or

20 R^3 does not represent C_1 - C_6 alkyl optionally substituted with one or more fluoro substituents or with C_3 - C_6 cycloalkyl; C_3 - C_5 cycloalkyl; C_3 - C_6 alkenyl; or C_3 - C_6 alkynyl; or

R_4 does not represent C_1 - C_4 alkyl optionally substituted with OH, NR^9R^{10} , CN, $CONR^9R^{10}$, $SO_2NR^9R^{10}$ or CO_2R^6 wherein R^6 is H or C_1 - C_4 alkyl and R^9 and R^{10} are each independently H or C_1 - C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-substituted piperizinyl or imidazolyl group wherein said group is optionally substituted with C_1 - C_4 alkyl or OH; C_2 - C_4 alkenyl optionally substituted with CN, $CONR^9R^{10}$ or CO_2R^6 ; C_2 - C_4 alkanoyl optionally substituted with NR^9R^{10} ; $(C_2-C_4)OH$ optionally substituted with NR^9R^{10} ; $(C_2-C_3)alkoxy(C_1-C_2)alkyl$ optionally substituted with OH or NR^9R^{10} .

which compounds are referred to together hereinafter as "the compounds of the invention".

The term "aryl", when used herein, includes six- to ten-membered carbocyclic aromatic groups, such as phenyl and naphthyl.

The term "Het", when used herein, includes four- to twelve-membered, preferably four- to ten-membered, ring systems, which rings contain one or more heteroatoms selected from nitrogen, oxygen, sulfur and mixtures thereof, and which rings may contain one or more double bonds or be non-aromatic, partly aromatic or wholly aromatic in character. The ring systems may be monocyclic, bicyclic or fused. The term thus includes groups such as optionally substituted azetidiny, pyrrolidiny, imidazolyl, indolyl, furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxatriazolyl, thiatriazolyl, pyridazinyl, morpholinyl, pyrimidinyl, pyrazinyl, pyridinyl, quinolinyl, isoquinolinyl, piperidinyl, pyrazolyl, imidazopyridinyl and piperazinyl. Substitution at Het may be at a carbon atom of the Het ring or, where appropriate, at one or more of the heteroatoms.

"Het" groups may also be in the form of an *N*-oxide.

The heterocyclic ring that R^3 and R^5 , R^7 and R^8 , R^9 and R^{10} , R^{13} and R^{14} or R^{15} and R^{16} (together with the nitrogen atom to which they are bound) may represent may be any heterocyclic ring that contains at least one nitrogen atom, and which ring forms a stable structure when attached to the remainder of the molecule *via* the essential nitrogen atom (which, for the avoidance of doubt, is the atom to which R^3 and R^5 , R^7 and R^8 , R^9 and R^{10} , R^{13} and R^{14} or R^{15} and R^{16} are attached). In this respect, heterocyclic rings that R^3 and R^5 , R^7 and R^8 , R^9 and R^{10} , R^{13} and R^{14} or R^{15} and R^{16} (together with the nitrogen atom to which they are bound) may represent include four- to twelve-membered, preferably four- to ten-membered, ring systems, which rings contain at least one nitrogen atom and optionally contain one or more further heteroatoms selected from nitrogen, oxygen and/or sulfur, and which rings may contain one or more double bonds or

be non-aromatic, partly aromatic or wholly aromatic in character. The term thus includes groups such as azetidiny, pyrrolidiny, imidazolyl, indolyl, triazolyl, tetrazolyl, morpholinyl, piperidiny, pyrazolyl and piperazinyl.

- 5 The term "C₁-C₆ alkyl" (which includes the alkyl part of alkylHet and alkylaryl groups), when used herein, includes methyl, ethyl, propyl, butyl, pentyl and hexyl groups. Unless otherwise specified, alkyl groups may, when there is a sufficient number of carbon atoms, be linear or branched, be saturated or unsaturated or be cyclic, acyclic or part cyclic/acyclic. Preferred C₁-C₆ alkyl groups for use
10 herein are C₁-C₃ alkyl groups. The terms "C₂-C₆ alkenyl" and "C₂-C₆ alkynyl", when used herein, include C₂-C₆ groups having one or more double or triple carbon-carbon bonds, respectively. Otherwise, the terms "C₂-C₆ alkenyl" and "C₂-C₆ alkynyl" are defined in the same way as the term "C₁-C₆ alkyl". Similarly, the term "C₁-C₆ alkylene", when used herein, includes C₁-C₆ groups which can be
15 bonded at two places on the group and is otherwise defined in the same way as "C₁-C₆ alkyl". The term "acyl" includes C(O)-(C₁-C₆)alkyl.

Substituted alkylHet and alkylaryl as defined hereinbefore may have substituents on the ring and/or on the alkyl chain.

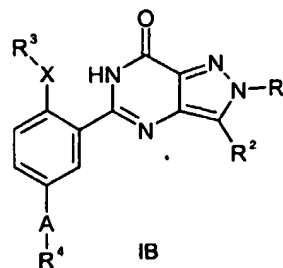
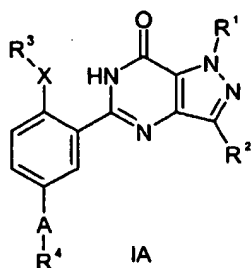
20

Halo groups with which the above-mentioned groups may be substituted or terminated include fluoro, chloro, bromo and iodo.

Compounds of general formula (I) can be represented by formulae IA and

25

IB:



wherein R^1 , R^2 , R^3 , R^4 , A and X are as defined hereinbefore.

A preferred group of compounds according to a further aspect of the invention,
5 are compounds of formulae IA or IB as hereinbefore defined, wherein:

X represents O;

A represents C(O) or CH(OH);

10

R^1 represents C_1 - C_6 alkyl substituted and/or terminated with OR^6 , $C(O)OR^6$, $C(O)NR^9R^{10}$ or NR^9R^{10} wherein said latter four groups are optionally substituted and/or terminated as defined hereinbefore;

or

15 R^1 represents Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl optionally substituted and/or terminated with one or more substituents selected from halo, C_1 - C_6 alkyl, OR^6 , $C(O)OR^6$, $C(O)NR^9R^{10}$ and NR^9R^{10} wherein said latter five groups are optionally substituted and/or terminated as defined hereinbefore;

20 R^2 and R^3 independently represent C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl optionally substituted and/or terminated with one or more substituents selected from halo, OR^6 , $C(O)OR^6$ and NR^9R^{10} wherein said latter three groups are optionally substituted and/or terminated as defined hereinbefore;

25 R^4 represents C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl optionally substituted and/or terminated with one or more substituents selected from halo and OR^6 wherein said OR^6 group is optionally substituted and/or terminated as defined hereinbefore;

wherein R^6 , R^9 and R^{10} are as hereinbefore defined.

30

A highly preferred group of compounds herein are those wherein:

A represents C(O) or CH(OH);

X represents O;

- 5 R¹ represents C₁-C₆ alkyl or C₁-C₆ alkylaryl wherein both groups are substituted and/or terminated with one or more substituents selected from halo, NR⁹R¹⁰, C(O)OR⁶ or C(O)NR⁹R¹⁰

or

- 10 R¹ represents Het or C₁-C₆ alkylHet wherein both groups are optionally substituted and/or terminated with one or more substituent groups selected from halo, OR⁶, C₁-C₆ alkyl and NR⁹R¹⁰;

- R² represents C₁-C₆ alkyl optionally substituted and/or terminated with one or
15 more substituent groups selected from halo and OR⁶;

or

- R² represents aryl or Het optionally substituted and/or terminated with one or
20 more substituent groups selected from halo, OR⁶ and NR⁹R¹⁰;

- R³ represents C₁-C₆ alkyl, Het, C₁-C₆ alkylHet, aryl or C₁-C₆ alkylaryl optionally substituted and/or terminated with one or more substituents selected from halo and OR⁶;

25

- R⁴ represents C₁-C₆ alkyl optionally substituted and/or terminated with one or more substituents selected from halo and OR⁶;

wherein R⁶, R⁹ and R¹⁰ are as hereinbefore defined.

30

A further preferred group of compounds are those wherein:

A represents C(O) and X represents O;

R¹ represents C₁-C₆ alkyl optionally substituted and/or terminated with one or
5 more substituent groups selected from OR⁶, C(O)OR⁶ and C(O)NR⁹R¹⁰;

or

R¹ represents Het or C₁-C₆ alkylHet optionally substituted and/or terminated with
one or more substituent groups selected from C₁-C₆ alkyl, OR⁶, C(O)OR⁶ and
C(O)NR⁹R¹⁰;

10

R² represents C₁-C₆ alkyl optionally substituted and/or terminated with one or
more substituent groups selected from halo and OR⁶;

R³ represents C₁-C₆ alkyl optionally substituted and/or terminated with one or
15 more substituents selected from halo and OR⁶;

R⁴ represents C₁-C₆ alkyl optionally substituted and/or terminated with one or
more substituents selected from halo and OR⁶;

20 wherein R⁶, R⁹ and R¹⁰ are as hereinbefore defined.

An additional preferred group of compounds are those wherein:

A represents C(O) and X represents O;

25

R¹ represents C₁-C₄ alkyl, an azetidiny group substituted and/or terminated with
one or more substituent groups selected from C₃-C₄ alkyl, OR⁶, C(O)OR⁶ and
C(O)NR⁹R¹⁰;

or

30

R^1 represents a (C₁-C₆)pyridinyl group which may be optionally substituted with one or more substituent groups selected from C₃-C₄ alkyl, OR⁶, C(O)OR⁶ and C(O)NR⁹R¹⁰;

- 5 R^2 represents C₁-C₃ alkyl optionally substituted and/or terminated with one or more substituent groups selected from halo and OR⁶;

R^3 represents C₁-C₄ alkyl optionally substituted and/or terminated with one or more substituents selected from halo and OR⁶;

10

R^4 represents C₁-C₃ alkyl optionally substituted and/or terminated with one or more substituents selected from halo and OR⁶;

- 15 wherein R⁶ is H or a C₁-C₄ alkyl group and wherein R⁹ and R¹⁰ are independently selected from methyl or ethyl groups.

An especially preferred group of compounds are those wherein:

A represents C(O) and X represents O;

20

R^1 represents C₂-C₃ alkyl group substituted and/or terminated with one or more substituent groups selected from OR⁶ or C(O)OR⁶;

- 25 R^2 represents C₂-C₃ alkyl, and is preferably ethyl, optionally substituted and/or terminated with one or more substituent groups selected from halo and OR⁶;

R^3 represents C₃-C₄ alkyl, and is preferably propyl, optionally substituted and/or terminated with one or more substituents selected from halo and OR⁶;

- 30 R^4 represents C₁-C₂ alkyl, and is preferably ethyl, optionally substituted and/or terminated with one or more substituents selected from halo and OR⁶;

wherein R⁶ is H or a C₂-C₄ alkyl group.

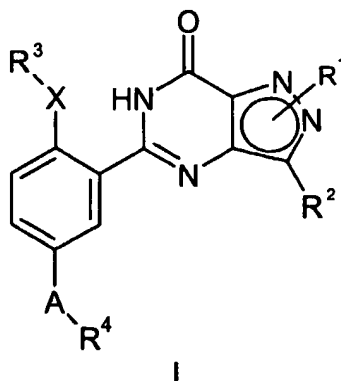
Especially preferred herein are compounds of formula 1 as described in the
5 Examples section herein and in particular:

- 5-(5-Acetyl-2-butoxyphenyl)-2-(1-cyclobutyl-3-azetidiny)-3-ethyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
tert-Butyl-5-[(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-1-yl]-acetate ;
10 *tert*-Butyl-5-[(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl]-acetate;
tert-Butyl-3-[(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-1-yl]-2-methylpropanoate;
15 Ethyl-2-[5-(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d] pyrimidin-2-yl]propanoate;
Methyl-4-[5-(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-1-yl]-butanoate;
Methyl-4-[5-(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-1-yl]-butanoate;
20 4-[5-(5-Acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-1-yl]butanoic acid;
4-[5-(5-Acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl]butanoic acid;
25 2-[5-(5-Acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl]-*N,N*-dimethylacetamide

and pharmaceutically acceptable salts, solvates and polymorphs thereof.

30 The present invention additionally provides compounds of general formula I:

12



or pharmaceutically or veterinarily acceptable salts, solvates, polymorphs or pro-drugs thereof wherein:

5

A represents C(O) or CH(OH);

X represents O or NR⁵;

- 10 R¹, R³, R⁴ and R⁵ independently represent H, C₁-C₆ alkyl, Het, C₁-C₆ alkylHet, aryl or C₁-C₆ alkylaryl (which latter five groups may all be optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR⁶, OC(O)R⁶, C(O)R⁶, C(O)OR⁶, NR⁶C(O)NR⁷R⁸, NR⁶C(O)OR⁶, OC(O)NR⁷R⁸, C(O)NR⁹R¹⁰, NR⁹R¹⁰, SO₂NR⁹R¹⁰, SO₂R¹¹, C₁-C₆ alkyl, Het, C₁-C₆ alkylHet, aryl
- 15 or C₁-C₆ alkylaryl wherein said latter five substituent and/or terminal groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR¹², OC(O)R¹², C(O)R¹², C(O)OR¹², NR¹²C(O)NR¹³R¹⁴, NR¹²C(O)OR¹², OC(O)NR¹³R¹⁴, C(O)NR¹⁵R¹⁶, NR¹⁵R¹⁶, SO₂NR¹⁵R¹⁶, SO₂R¹⁷); or R³ and R⁵ together with the nitrogen atom to which they
- 20 are bound can form a heterocyclic ring which is optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR¹², OC(O)R¹², C(O)R¹², C(O)OR¹², NR¹²C(O)NR¹³R¹⁴, NR¹²C(O)OR¹², OC(O)NR¹³R¹⁴, C(O)NR¹⁵R¹⁶, NR¹⁵R¹⁶, SO₂NR¹⁵R¹⁶, SO₂R¹⁷;
- 25 R² represents H, halo, cyano, nitro, OR⁶, OC(O)R⁶, C(O)R⁶, C(O)OR⁶, NR⁶C(O)NR⁷R⁸, NR⁶C(O)OR⁶, OC(O)NR⁷R⁸, C(O)NR⁹R¹⁰, NR⁹R¹⁰, SO₂NR⁹R¹⁰, SO₂R¹¹, C₁-C₆ alkyl, Het, C₁-C₆ alkylHet, aryl or C₁-C₆ alkylaryl (which latter five

- groups may all be optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR^6 , $OC(O)R^6$, $C(O)R^6$, $C(O)OR^6$, $NR^6C(O)NR^7R^8$, $NR^6C(O)OR^6$, $OC(O)NR^7R^8$, $C(O)NR^9R^{10}$, NR^9R^{10} , $SO_2NR^9R^{10}$, SO_2R^{11} , C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl wherein said latter
- 5 five substituent and/or terminal groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17});
- 10 R^6 represents H, C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl (which latter five groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17});
- 15 R^7 and R^8 independently represent H, C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl (which latter five groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17}); or R^7 and R^8 together with the nitrogen atom to which they are bound can form a heterocyclic ring;
- 20 R^9 and R^{10} independently represent H, $C(O)R^6$, SO_2R^{11} , C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl (which latter five groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17}); or R^9 and R^{10} together with the nitrogen atom to which they are bound can form a
- 30 heterocyclic ring;
- R^{11} represents a C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl group is optionally substituted and/or terminated with one or more substituents selected

from halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17} ;

R^{12} represents H or C_1 - C_6 alkyl;

5

R^{13} and R^{14} independently represent H or C_1 - C_6 alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are bound can form a heterocyclic ring;

R^{15} and R^{16} independently represent H, $C(O)R^{12}$, SO_2R^{17} or C_1 - C_6 alkyl; or R^{15} and R^{16} together with the nitrogen atom to which they are bound can form a heterocyclic ring;

wherein when R^7 and R^8 , or R^9 and R^{10} together with the nitrogen atom to which they are bound form a heterocyclic ring, said heterocyclic ring is optionally substituted and/or terminated with one or more substituents selected from: halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17} ;

R^{17} represents C_1 - C_6 alkyl;

20

Het represents an optionally substituted four- to twelve-membered heterocyclic group, which group contains one or more heteroatoms selected from nitrogen, oxygen, sulphur and mixtures thereof;

with the proviso that when X represents O then R^1 does not represent H, unsubstituted C_1 - C_6 alkyl or C_1 - C_6 alkyl substituted and/or terminated by one or more halo substituents.

The compounds of formula I, and their pharmaceutically acceptable salts, have the advantage that they are inhibitors of the cGMP PDE5 enzyme, they have desirable potency, they demonstrate desirable selectivity or have other more desirable properties versus the compounds of the prior art

30

For successful utility within the pharmaceutical industry it is desirable that an active material should have good physical chemical properties, such as for example solubility. In some cases compounds can exhibit desirable medicinal properties which cannot be translated directly into a suitable pharmaceutical composition because the active compound itself has unsatisfactory physical properties such as for example poor chemical or processing properties.

The highly preferred compounds herein demonstrate desirable solubility characteristics in conjunction with desirable pharmacological properties, potency and selectivity.

Compounds of general formulae (I), (IA) or (IB) are referred to herein after as "the compounds of the invention" or "the compounds".

The pharmaceutically or veterinarily acceptable salts of the compounds which contain a basic centre are, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulphuric and phosphoric acid, with carboxylic acids or with organo-sulphonic acids. Examples include the HCl, HBr, HI, sulphate or bisulphate, nitrate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, saccharate, fumarate, maleate, lactate, citrate, tartrate, gluconate, camsylate, methanesulphonate, ethanesulphonate, benzenesulphonate, p-toluenesulphonate and pamoate salts. Compounds of the invention can also provide pharmaceutically or veterinarily acceptable metal salts, in particular non-toxic alkali and alkaline earth metal salts, with bases. Examples include the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts. For a review on suitable pharmaceutical salts see Berge *et al*, J. Pharm, Sci., 66, 1-19, 1977.

The pharmaceutically acceptable solvates of the compounds include the hydrates thereof.

Also included within the scope herein are various salts of the compounds and polymorphs thereof.

Where a compound contains one or more asymmetric carbon atoms it therefore exists in two or more stereoisomeric forms. Where a compound contains an alkenyl or alkenylene group, cis (E) and trans (Z) isomerism may also occur. The present invention includes the individual stereoisomers of the compound and, where appropriate, the individual tautomeric forms thereof, together with mixtures thereof. Separation of diastereoisomers or cis and trans isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate. All stereoisomers of the compounds are included within the scope herein.

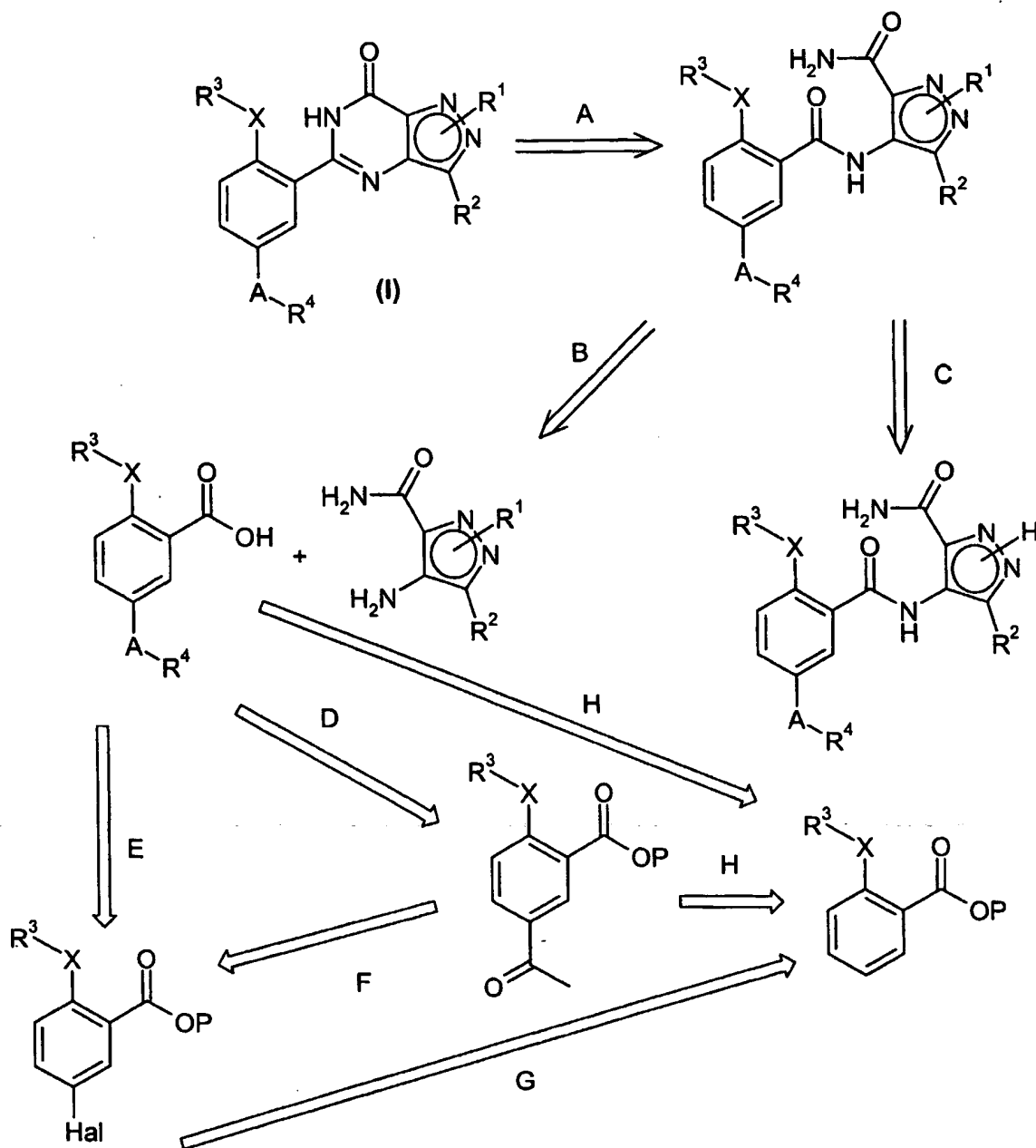
The compounds may exhibit tautomerism. All tautomeric forms of the compounds, and mixtures thereof, are included within the scope herein.

Also included within the scope of the application are radiolabelled derivatives of the compounds which are suitable for biological studies.

Preparation

The compounds may be prepared in accordance with the methods detailed in the example and preparations section herein after. More specifically, routes by which the compounds herein may be prepared are as illustrated in Schemes 1, 2, 3 and 4 below:

SCHEME 1



5

In the compounds of Scheme 1 R¹, R², R³, R⁴, A and X are as hereinbefore defined, P is either H or a protecting group, such as for example a methyl, ethyl or n-butyl group and Hal is a halogen, preferably Br or I. When P is an ester protecting group such group may be readily converted to the corresponding acid

10 via suitable hydrolysis.

The compounds of Scheme 1 wherein A = CH(OH) can be prepared from the compounds of Scheme 1 wherein A = C(O) at any suitable stage in the route illustrated. Such transformation may be effected *via* use of a suitable reducing agent, preferably sodium borohydride in methanol. The reverse transformation
5 can be effected *via* use of suitable oxidising conditions, such as for example magnesium dioxide oxidation.

The cyclodehydration reaction of Step A may be accomplished under basic, neutral or acidic conditions using known methods for pyrimidone ring formation.
10 Preferably, the cyclisation is performed under either basic conditions such as by using an alkali metal salt of an alcohol or amine, such as sodium ethoxide, potassium *tert*-butoxide, cesium carbonate or potassium bis(trimethylsilyl)amide, in the presence of a suitable alcoholic solvent, such as ethanol, for example at reflux temperature and optionally elevated pressure (or, if performed in a sealed
15 vessel, at greater than reflux temperature), or the cyclisation can be performed under acidic conditions using polyphosphoric acid. The skilled person will appreciate that, when X represents O and an alcohol is selected as solvent, an appropriate alcohol of formula R³OH, may be used if it is intended to mitigate alkoxide exchange at the 2-position of the phenyl.

20

In general, Step A can be base mediated by using an alkali metal salt such as for example Cs₂CO₃, K₂CO₃, potassium bis(trimethylsilyl)amide (KHMDs) or KO^tBu, in an alcoholic solvent, preferably of formula R³OH, or using a sterically hindered alcohol as solvent (e.g. 3-methyl-3-pentanol) at between about 70°C to the reflux
25 temperature of the selected solvent, for from 6 to about 30 hours, optionally at elevated pressure and optionally in the presence of a hydroxide scavenger, preferably R³OAc.

Similarly, Step A can be acid mediated such as by treatment with either
30 polyphosphoric acid at from about 130 to about 150°C or with a Lewis acid, e.g. anhydrous zinc chloride at from about 200 to about 220°C.

Preferably Step A is carried out with from about 2 to 3 equivalents of Cs_2CO_3 or KO^tBu in R^3OH , optionally in the presence of about 1 to 2 equivalents of R^3OAc , at the reflux temperature of the solvent, and optionally at elevated pressure, for between about 6 hours and about 5 days.

5

When X-R^3 is $-\text{OR}^3$ in the compound obtained from Step A, then it is possible to start Step A from a compound having either an $-\text{OR}^3$ or an $-\text{OR}^{3a}$ group wherein $-\text{OR}^{3a}$ represents $-\text{OR}^3$ or any alternative alkoxy group which is replaceable by $-\text{OR}^3$. Suitable OR^{3a} groups include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy and any other alkoxy group capable of being exchanged for $-\text{OR}^3$ wherein R^3 is as defined hereinbefore. As defined herein OR^{3a} , for example when $-\text{OR}^3$ is ethoxy may either be ethoxy or be any alternative alkoxy group which is replaceable by ethoxy.

10

15 The coupling reaction of Step B may be achieved by conventional amide bond forming techniques which are well known to those skilled in the art. For example, an acyl halide (e.g. chloride) derivative of the starting benzoic acid with the pyrazole compound in the presence of an excess of a tertiary amine, such as triethylamine or pyridine, optionally in the presence of a suitable catalyst, such as
20 4-dimethylaminopyridine, in a suitable solvent such as dichloromethane or THF, at a temperature of about 0°C to room temperature.

A variety of other amino acid coupling methodologies may be used to couple the benzoic acid compounds to the pyrazole compounds illustrated in Scheme 1.

25 For example, the acid or a suitable salt thereof (e.g. sodium salt) may be activated with an appropriate activating reagent, e.g. a carbodiimide, such as 1,3-dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride optionally in the presence of 1-hydroxybenzotriazole hydrate and/or a catalyst such as 4-dimethylaminopyridine; a halotrisaminophosphonium
30 salt such as bromo-tris(pyrrolidinyl)phosphonium hexafluorophosphate; a suitable pyridinium salt such as 2-chloro-1-methyl pyridinium chloride; or another suitable coupling agent such as O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium hexafluorophosphate (HATU). Either type of coupling reaction may be

conducted in a suitable solvent such as dichloromethane, tetrahydrofuran or *N,N*-dimethylformamide, optionally in the presence of a tertiary amine such as *N*-methylmorpholine or *N*-ethyldiisopropylamine (for example when either the pyrazole compound, or the activating agent is presented in the form of an acid addition salt), at from about 0°C to about room temperature. Preferably, from about 1 to 2 molecular equivalents of the activating reagent and from 1 to 3 molecular equivalents of any tertiary amine present may be employed.

Alternatively, the carboxylic acid function of the benzoic acid compound may be activated using an excess of a suitable acid acceptor reagent such as *N,N'*-carbonyldiimidazole in an appropriate solvent, e.g. ethyl acetate, dichloromethane or butan-2-one, at from about room temperature to about 80°C, followed by reaction of the intermediate imidazolide with a pyrazole compound at from about 20°C to about 90°C.

In a further variation, the final cyclised compound (of general formula (I), (IA) or (IB), as defined previously herein and as illustrated in the general process of Scheme 1), may be formed in a one-pot procedure by coupling the pyrazole compound and the acyl chloride derivative of the benzoic acid illustrated in Scheme 1 and by cyclising the resultant intermediate compound using the methods as described previously. The one-pot procedure may further involve an *in-situ* coupling and cyclisation reaction to form a compound of formula (I), (IA) or (IB). Preferably, pyridine may serve as an acid scavenger and as the solvent for the *in-situ* coupling and cyclisation reaction.

Typical conditions for Step B require the acid chloride (of the benzoic acid compound), the pyrazole compound and trimethylamine or pyridine at from 0°C to about room temperature for up to about 16 hours. Alternative conditions for Step B require the acid, the pyrazole compound, O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluor-phosphate (HATU reagent)/(PyBOP®) Benzotriazol-1-yloxytris(pyrrolidino) phosphonium hexafluorophosphate / (PYBrOP) bromo-tris-pyrrolidino-phosphonium hexafluorophosphate / Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide) or 1-(3-

dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSCDI) / N,N'-dicyclohexylcarbodiimide (DCC) and (HOBT) / 1-hydroxy-7-azabenzotriazole (HOAT), with an excess of N-methyl morpholine (NMM), or triethylamine, or Hünigs base in THF, dichloromethane or ethyl acetate, at room temperature for
5 from about 1 to about 48 hrs.

Preferred conditions for Step B are using about 1 equivalent of the acid chloride and about 1 equivalent of the pyrazole with an excess (about 3 equivalents) of triethylamine in dichloromethane for about 3 hours at room temperature.

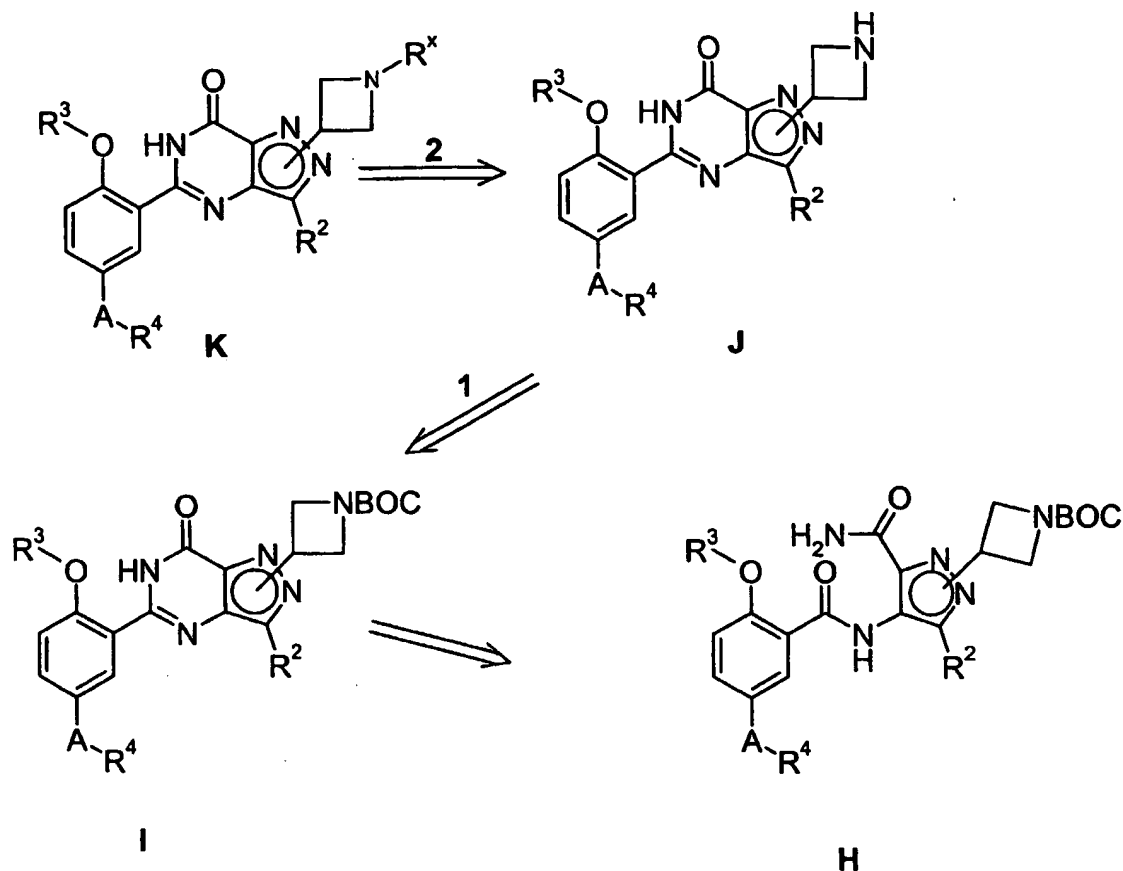
10

Step C is an alkylation reaction with R^1L , where L is a suitable leaving group, such as halo, tosylate, mesylate, in the presence of a base, optionally in the presence of a catalyst, in a solvent at between 0°C and the reflux temperature of
15 the solvent. Typical conditions utilise a slight excess of R^1L , a slight excess of base, such as K_2CO_3 or Cs_2CO_3 , in DMF or MeCN, at between about 40°C and about 100°C.

Preferred conditions for Step C use from about 1.2 to about 2 equivalents of R^1L ,
20 (wherein L is preferably Cl, I or mesylate or tosylate), and from about 1.2 to about 1.5 equivalents of Cs_2CO_3 , in DMF at between about 50°C and about 90°C for from about 16 to about 34 hours.

In Step C the R^1 group may be a protected group as illustrated below:

25



Step D provides functionalisation at a position alpha to the ketone substituent (at the 5' position on the phenyl ring). Such functionalisation of for example a methyl ketone to a substituted methyl ketone can occur at any step and in any route. Step D applies when A represents C=O and R⁴ represents methylene substituted with groups defined hereinbefore. Using standard conditions to enable halogenation, preferably bromination, alpha- to the ketone to form alpha-halo ketones, or conditions to enable oxidation alpha- to the ketone where the resulting alpha-hydroxy group is converted to a leaving group. The halogen or oxygenated leaving group can then be displaced by a suitable nucleophile, e.g. primary or secondary amine.

Preferred conditions for step D are bromination using about 1.1 equivalent of *N*-bromosuccinimide, about 3 equivalents of triflic acid and dichloromethane. Alternatively, addition of a base will allow formation of the enolate, which can then be quenched on to a suitable electrophile (e.g. lower alkyl halide). Typical conditions for such transformation are from about 1.1 to about 2 equivalents of

suitable base (e.g. LDA, NaH), from about 1.1 to about 2 equivalents of suitable electrophile (e.g. lower alkyl halides) in THF or ether followed by reaction with an R^4L group wherein L is a suitable leaving group. Advantageously, during Step D ester hydrolysis can also occur thereby enabling acid coupling with the pyrazole amine following isolation of the acidic product.

These transformations can occur when P = H or protecting group (as detailed hereinbefore).

- 10 Step E introduces a functionalised ketone moiety into the phenyl compound. Conversion of Hal to A- R^4 can occur at any step in any of the routes. This can be achieved by any one of the routes outlined below:-
- (a) so-called "Heck" conditions (e.g. 2 eq. of a source of an acyl anion equivalent (such as butyl vinyl ether), 1.7 eq. of Et_3N and catalytic amounts of $Pd(OAc)_2$ and P(o-tol)₃, in MeCN at between room temperature and reflux). Performing a Heck reaction on an alkyl alkenyl ether (will give products where A represents C=O). Such reactions are not suitable when R^4 is aryl; or
- 15 (b) so-called "Sonogashira" conditions (for example as described in *Synthesis* 1980, 8, 627, such as 1.5 to 5 eq. of a terminal alkyne and 0.024 to 0.03 eq. of $Pd(PPh_3)_2Cl_2$ / CuI, in Et_3N and MeCN at between room temperature and 60°C), followed by hydrolysis of the resultant alkyne (typical conditions 0.3 equiv. $HgSO_4$, H_2SO_4 , acetone at reflux). Note, this procedure will give products where A represents C=O. Such reactions are not suitable when R^4 is aryl; or
- 20 (c) Halogen/ lithium exchange followed by quenching onto an acyl chloride (to give products where A represents C=O). Alternatively, the anion could be quenched onto an aldehyde to give products where A represents CH(OH). This alcohol could then be re-oxidised to the corresponding ketone by methods described hereinbefore. Preferred conditions for acyl chloride reaction: 1 – 2 equivalents of n-Butyl Lithium, 1 – 2 equivalents of R^4COCl , THF, at from about -78°C to about room temperature. If for example R^4COCl is LCH_2COCl (where L is a leaving group as defined earlier), then once the above procedure has been performed the product can be further
- 25
- 30

functionalised by displacement of L with a nucleophile (e.g. primary or secondary amine)

- (d) Formation of Grignard or zincate through addition of magnesium or a zinc source (e.g. zinc, zinc chloride, Reike zinc), followed by quenching onto an acyl chloride (to give products where A represents C=O). Alternatively the Grignard or zinc reagent could be quenched onto an aldehyde to give products where A represents CH(OH). Again, the alcohol formed could be oxidised to give the required ketone as detailed hereinbefore.
- (e) Carbonylation to yield a carboxylic acid, ester, or Weinreb amide. Preferred conditions: CO (50psi), Pd(OAc)₂ (0.03eq.), 1,1'-bis(diphenylphosphino)ferrocene (0.045eq.), triethylamine (5eq.), and suitable nucleophile (e.g. alcohol, amine) at from 40 to about 80°C. Alternatively the Weinreb amide can be synthesised from the carboxylic acid and the aldehyde could be synthesised from the ester or carboxylic acid. The acid chloride can be formed from the carboxylic acid. Preferred conditions to form acid chloride from acid: (COCl)₂ (1.2eq.), DMF (drop), DCM. A nucleophile such as a Grignard reagent or zincate can then be reacted with the ester, Weinreb amide or acid chloride to yield products where A represents C=O. Alternatively, analogous reactions with the aldehyde would yield products where A represents CH(OH). Preferred conditions for addition of Grignard reagent into acid chloride: R⁴MgBr (1eq.), Fe(acac)₃ (0.03eq.), THF.

Advantageously, during Step E "in-situ" hydrolysis of the ester protecting group can occur thereby enabling acid coupling with the pyrazole amine following isolation of the acidic product.

These transformations can occur when P = H or protecting group (as detailed hereinbefore).

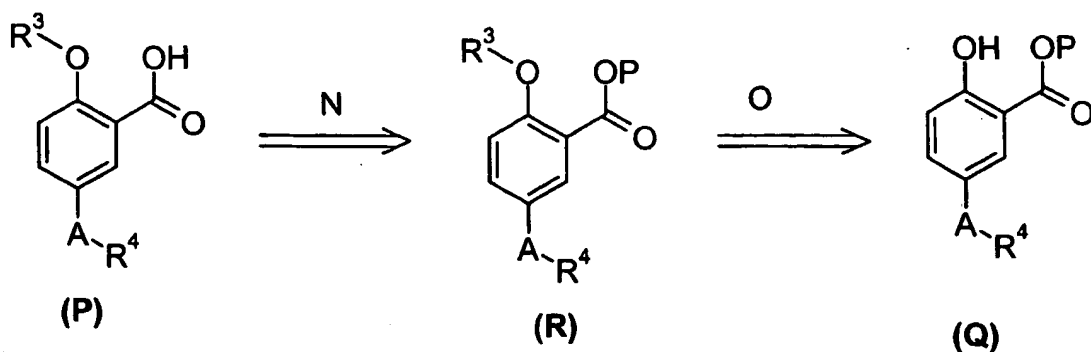
- Step F illustrates the formation of a methyl ketone from the appropriate halogenated phenyl compound. Conversion of Hal to C(O)Me can occur at any step in any of the routes, by the methods outlined in E(a) to (e) above.

Step G illustrates the halogenation of 2-alkoxy benzoates wherein Hal represents Cl, Br or I, preferably Br or I. Typical conditions for halogenation are *N*-iodosuccinimide (1 to 2eq.), trifluoroacetic acid:trifluoroacetic anhydride (4:1 mixture as solvent) at temperatures between room temperature and reflux. Once
5 halogenation has occurred the 2-alkoxy substituent can be exchanged with alternative alkoxy or amino substituents. This 2' exchange reaction can also occur at any subsequent step in the synthesis of the compounds of general formula (I). Typical conditions for 2' exchange with alternative alkoxy substituents are Cs₂CO₃ (2 to 4eq.) or KO^tBu (1 to 3 eq.) or KHMDS (2 to 5 eq.),
10 ROH as solvent at temperatures between room temperature and reflux. Typical conditions for 2' exchange with amino substituents are copper sulphate (catalytic), R'R''NH₂ at temperatures between room temperature and reflux.

Step H provides for acylation at the C-5 position of the phenyl ring using Friedel
15 Crafts reactions (to give products where A represents C=O). Typical conditions: AlCl₃ (2 to 10 eq.), RCOCl (1 to 3 eq.), DCM at 0°C to reflux.

An alternative synthesis of the starting acid in reaction B (compound P), where A-R⁴ is acetyl can be accomplished in two steps (reactions O and N) from a
20 protected acid (compound Q) as illustrated below:

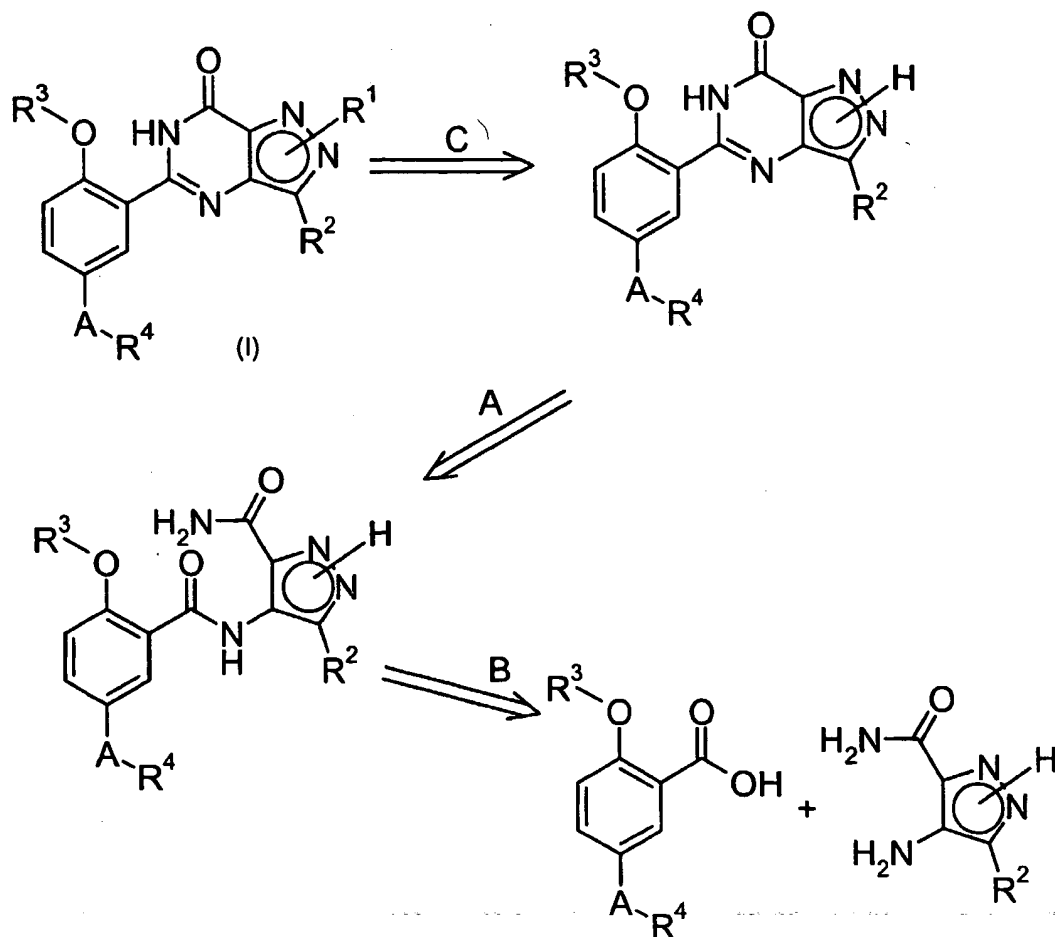
26



In Step N the protected acid R undergoes ester hydrolysis under standard conditions, typically using about 2 equivalents of sodium hydroxide in a dioxan : water mixture with a volume ratio of 10 : 1 at room temperature for about 18 hours.

In Step O the alkylation reaction (of the OH group) is typically accomplished by use of from about 4.5 to about 6 equivalents of R^3L wherein L is a suitable leaving group, and wherein L is preferably I, with about 3 to about 4.5 equivalents of a suitable base, such as K_2CO_3 in an appropriate solvent such as acetonitrile for 3 to 4 days at $60^\circ C$ to about $80^\circ C$.

Scheme 2 illustrates the preparation of the compounds via a process wherein the R^1 substituent is included as the final step.



5 In Scheme 2, A, X, R¹, R², R³ and R⁴ are as hereinbefore defined.

Step C is an alkylation reaction with R¹L, where L is a suitable leaving group, such as halo, tosylate, mesylate, in the presence of a base, optionally in the presence of a catalyst, in a solvent at between 0 and 40°C. Typical conditions
 10 utilise an excess of R¹L, a slight excess of base, such as K₂CO₃ or Cs₂CO₃, in DMF or MeCN, at between about 0 and about 40°C.

Preferred conditions for step C use from about 1.0 to about 1.1 equivalents of R¹L, (wherein L is preferably Cl), and about 1.4 to about 1.6, more preferably

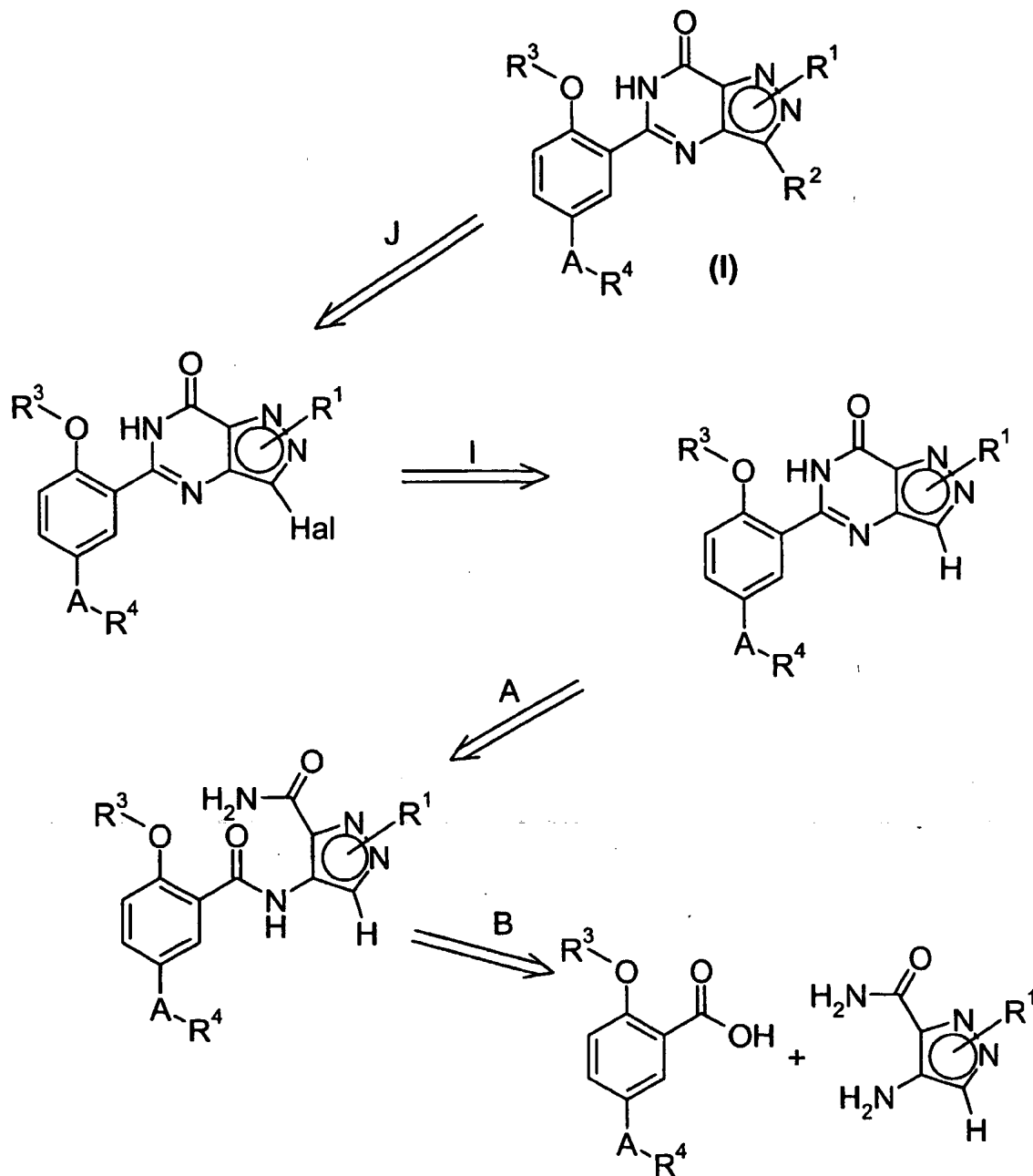
about 1.5 equivalents of Cs_2CO_3 in DMF at room temperature from 24 to about 72 hours.

Steps A and B can be carried out using the conditions and reagents as detailed
5 herein before in relation to Scheme 1.

Illustrated in Scheme 3 is a general process whereby, when R^2 may be added to the general structure.

10

SCHEME 3



In Scheme 3, A, X, R^1 , R^2 , R^3 and R^4 are as hereinbefore defined and Hal is Cl,
5 Br or I.

Step I provides for halogenation at the C-3 position on the pyrazole ring. In Step I, Hal represents Cl, Br or I in this instance and is preferably Br. Typical conditions for bromination are bromine (1.5 to 2 equiv.) and sodium acetate (1.5

to 2 equiv.) in a suitable solvent (e.g. acetic acid) at temperatures between room temperature and the reflux temperature of the solvent. Optionally, this halogenation step can be performed at other stages in the reactions sequence illustrated in Scheme 3 (i.e. before cyclisation or before coupling).

5

In Step J, wherein Hal = I, Pd coupling is used to introduce the R² group. Such reagents are applicable where R² is alkyl, alkylHet, Het, Aryl or alkylAryl (all optionally substituted as defined hereinbefore), as well as cyano, C(O)R⁶ and C(O)O R⁶ (wherein R⁶ is as described hereinbefore) using coupling conditions

10 such as are known to those skilled in the art.

(a) so-called "Suzuki" conditions (e.g. 1.2 eq. of boronic acid, 2 eq. of K₂CO₃ and 0.1 eq. of Pd(PPh₃)₄, refluxing in an approximately 4:1 mixture of dioxane:water, or 2.5 to 3 eq. of CsF, 0.05 to 0.1 eq. of Pd₂(dba)₃ and 0.01 to 0.04 eq of P(o-tol)₃, refluxing in DME);

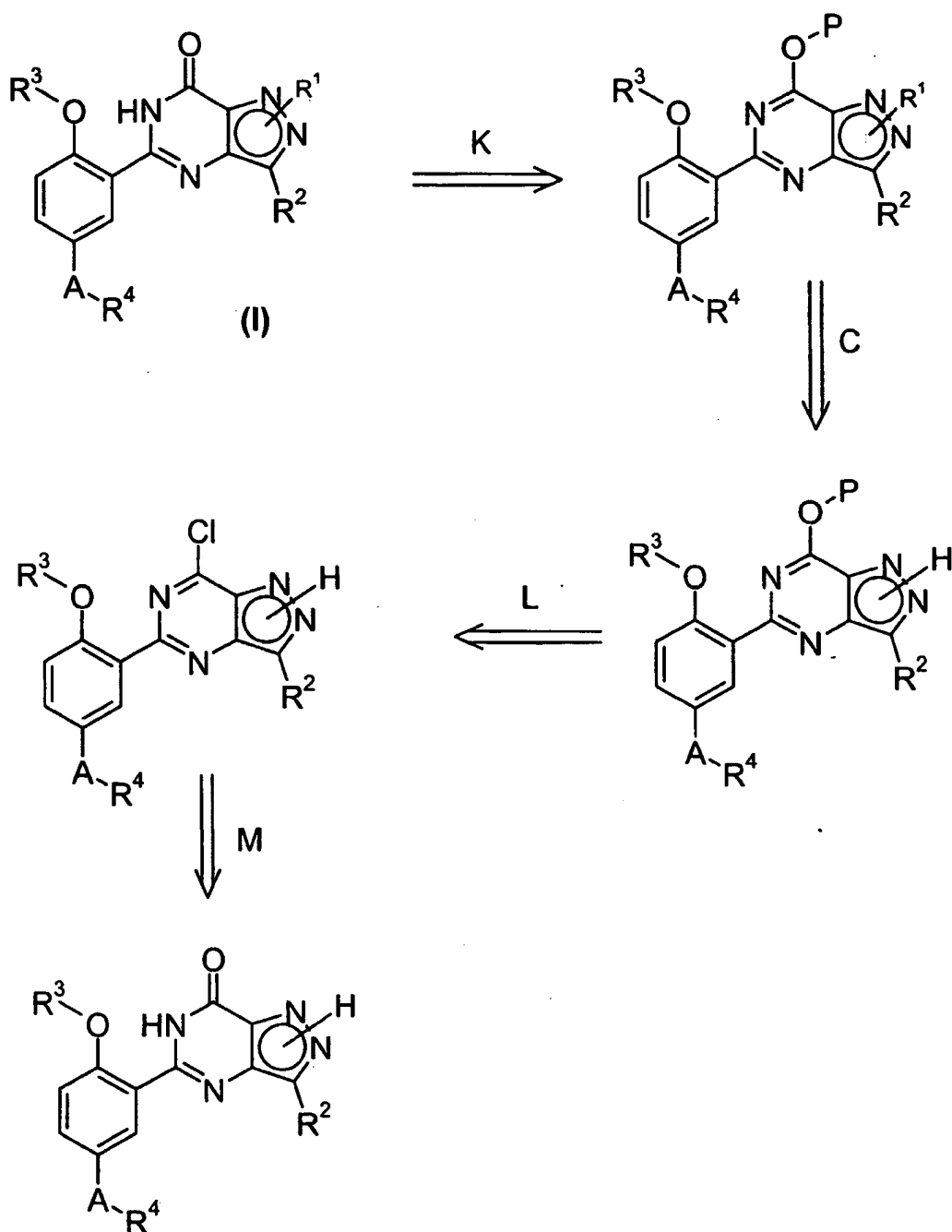
15 (b) so-called "Stille" conditions (e.g. 1.5 eq. of stannane, 10 eq. of LiCl, 0.15 eq. of CuI, and 0.1 eq. of Pd(PPh₃)₄, refluxing in dioxane, or 5 eq. of stannane, 3.6 eq. of Et₃N, Pd₂(dba) and P(o-tol)₃, refluxing in MeCN);20 (c) so-called "Heck" conditions (e.g. 2 eq. of a source of an acyl anion equivalent (such as butyl vinyl ether), 1.7 eq. of Et₃N and catalytic amounts of Pd(OAc)₂ and P(o-tol)₃, in MeCN at between room temperature and reflux); or25 (d) so-called "Sonogashira" conditions (for example as described in *Synthesis* 1980, 8, 627, such as 1.5 to 5 eq. of a terminal alkyne and 0.024 to 0.03 eq. of Pd(PPh₃)₂Cl₂ / CuI, in Et₃N and MeCN at between room temperature and 60°C); or30 (e) carbonylation conditions such as reaction with an appropriate palladium catalyst system (e.g. palladium(II) acetate combined with 1,2-bis(diphenylphosphino)-propane (DPPP)) under an atmosphere of carbon monoxide (e.g. at a pressure of around 482.6 kPa (70 psi)) in the presence of an excess of an alcohol, an excess of a tertiary amine base (e.g. Et₃N), and optionally in the presence of a suitable solvent (e.g. dimethylsulfoxide).

The skilled chemist would appreciate that the steps described above can be

carried out in any order, for example the conversion of Hal to $-AR^4$, optionally via C(O)Me, can take place either before or after coupling or before or after cyclisation.

- 5 Steps A and B are as hereinbefore detailed.

Scheme 4 illustrates a general process wherein compounds of formula (I) can be prepared from similar compounds wherein R^1 is introduced onto a protected pyrimidinone.

SCHEME 4

In Scheme 4, A, X, R¹, R², R³ and R⁴ are as hereinbefore defined.

- 5 Step K involves the removal of pyrimidinone protecting group wherein P is a hydroxy protecting group, preferably Me. Typical conditions for removing methyl are *via* use of 6M HCl at temperatures of between room temperature and about 70°C.

Step L introduces an alkoxy group onto the halogenated (chlorinated) pyrimidine ring. Typical conditions are to react the chloropyrimidine with POH (where P is defined as above) at between room and reflux temperature in the presence of a suitable base (e.g. potassium *tert*-butoxide).

Step M involves chlorination of pyrimidinone ring. Typical conditions are to react with a chlorinating agent (e.g. POCl₃) at between room and reflux temperature, optionally in a suitable solvent and optionally in the presence of from about 1 to about 2 equivalents of a suitable additive (e.g. N,N-dimethylformamide or N,N-dimethylaniline).

Protection / deprotection strategies as appropriate may be employed such as are known in the literature. Suitable protecting groups for use in accordance with the invention can be found in "Protecting Groups" edited by P.J. Kocienski, Thieme, New York, 1994; and "Protective Groups in Organic Synthesis" 2nd edition, T.W. Greene & P.G.M. Wutz, Wiley -Interscience (1991).

It will be appreciated by those skilled in the art that certain protected derivatives of compounds of formula (I), which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". Further, certain compounds of formula (I) may act as prodrugs of other compounds of formula (I).

All protected derivatives, and prodrugs, of compounds of formula (I) are included within the scope of the invention. Examples of suitable pro-drugs for the compounds of the present invention are described in Drugs of Today, Volume 19, Number 9, 1983, pp 499 – 538 and in Topics in Chemistry, Chapter 31, pp 306 – 316 and in "Design of Prodrugs" by H. Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are incorporated herein by reference).

It will further be appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as "pro-moieties", for example as described by H. Bundgaard in "design of Prodrugs" (the disclosure in which document is incorporated herein by reference) may be placed on appropriate functionalities
5 when such functionalities are present within compounds of formula (I).

Preferred prodrugs for compounds of formula (I) include : alcohols, esters, carbonate esters, hemi-esters, phosphate esters, nitro esters, sulfate esters, sulfoxides, amides, carbamates, azo-compounds, phosphamides, glycosides,
10 ethers, acetals and ketals.

Pharmaceutically acceptable acid addition salts of the compounds which contain a basic centre may be prepared in a conventional manner. For example, a solution of the free base may be treated with the appropriate acid, either neat or
15 in a suitable solvent, and the resulting salt may then be isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts can be obtained in an analogous manner by treating a solution of a compound with the appropriate base. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

20

The present application also includes all suitable isotopic variations of the compounds or pharmaceutically acceptable salts thereof. An isotopic variation of a compound or a pharmaceutically acceptable salt thereof is defined as one in which at least one atom is replaced by an atom having the same atomic number
25 but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into the compounds and pharmaceutically acceptable salts thereof include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine and chlorine such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively. Certain isotopic
30 variations of the compounds and pharmaceutically acceptable salts thereof, for example, those in which a radioactive isotope such as ^3H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of

preparation and detectability. Further, substitution with isotopes such as deuterium, i.e., ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances.

- 5 Isotopic variations of the compounds and pharmaceutically acceptable salts thereof of this invention can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the Examples and Preparations hereafter using appropriate isotopic variations of suitable reagents.

10

It will be appreciated by those skilled in the art that certain protected derivatives of the compounds, which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form

15 compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". Further, certain compounds may act as prodrugs of other compounds.

All protected derivatives, and prodrugs, of the compounds are included within the

20 scope.

The present invention additionally comprises the combination of a cGMP PDE₅ inhibitor compound as defined herein, wherein said combination can be administered by sequential, simultaneous or joint administration of a compound

25 with:

- (1) one or more naturally occurring or synthetic prostaglandins or esters thereof.

Suitable prostaglandins for use herein include compounds such as alprostadil, prostaglandin E₁, prostaglandin E₀, 13, 14 - dihydroprostaglandin

30 E₁, prostaglandin E₂, eprostinol, natural synthetic and semi-synthetic prostaglandins and derivatives thereof including those described in US 6,037,346 issued on 14th March 2000 and incorporated herein by reference, PGE₀, PGE₁, PGA₁, PGB₁, PGF₁ α , 19-hydroxy PGA₁, 19-hydroxy - PGB₁,

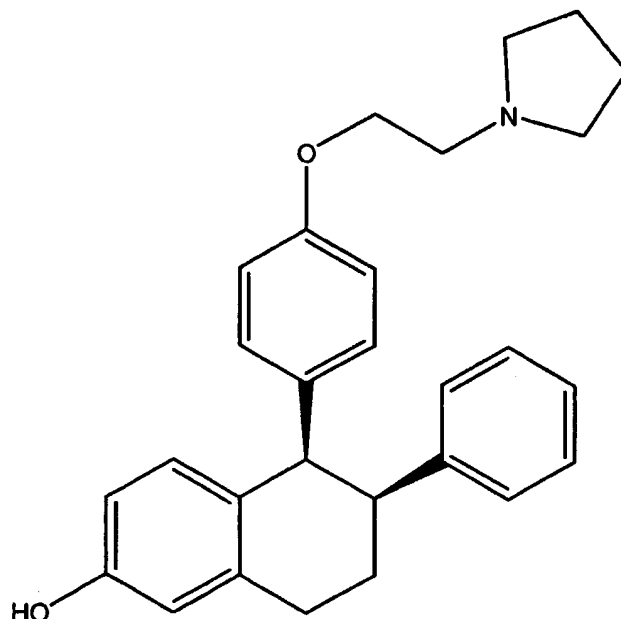
PGE₂, PGB₂, 19-hydroxy-PGA₂, 19-hydroxy-PGB₂, PGE₃ α , carboprost tromethamine dinoprost, tromethamine, dinoprostone, lipo prost, gemeprost, metenoprost, sulprostone, tiaprostone and moxislylate; and/or

- (2) one or more α - adrenergic receptor antagonist compounds also known as α - adrenoceptors or α -receptors or α -blockers. Suitable compounds for use herein include: the α -adrenergic receptors as described in PCT application WO99/30697 published on 14th June 1998, the disclosures of which relating to α -adrenergic receptors are incorporated herein by reference and include, selective α_1 -adrenoceptors or α_2 -adrenoceptors and non-selective adrenoceptors, suitable α_1 -adrenoceptors include: phentolamine, phentolamine mesylate, trazodone, alfuzosin, indoramin, naftopidil, tamsulosin, dapiprazole, phenoxylbenzamine, idazoxan, efaraxan, yohimbine, rauwolfia alkaloids, Recordati 15/2739, SNAP 1069, SNAP 5089, RS17053, SL 89.0591, doxazosin, terazosin, abanoquil and prazosin; α_2 -blockers from US 6,037,346 [14th March 2000] dibenamine, tolazoline, trimazosin and dibenamine; α -adrenergic receptors as described in US patents: 4,188,390; 4,026,894; 3,511,836; 4,315,007; 3,527,761; 3,997,666; 2,503,059; 4,703,063; 3,381,009; 4,252,721 and 2,599,000 each of which is incorporated herein by reference; α_2 -Adrenoceptors include: clonidine, papaverine, papaverine hydrochloride, optionally in the presence of a cariotonic agent such as pirxamine; and/or
- (3) one or more NO-donor (NO-agonist) compounds. Suitable NO-donor compounds for use herein include organic nitrates, such as mono- di or tri-nitrates or organic nitrate esters including glyceryl brinitrate (also known as nitroglycerin), isosorbide 5-mononitrate, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, sodium nitroprusside (SNP), 3-morpholinosydnonimine molsidomine, S-nitroso- N-acetyl penicillamine (SNAP) S-nitroso-N-glutathione (SNO-GLU), N-hydroxy - L-arginine, amyl nitrate, linsidomine, linsidomine chlorohydrate, (SIN-1) S-nitroso - N-cysteine, diazenium diolates,(NONOates), 1,5-pentanedinitrate, L-arginine, ginseng, zizphi fructus, molsidomine, Re - 2047, nitrosylated maxislyte

derivatives such as NMI-678-11 and NMI-937 as described in published PCT application WO 0012075 ; and/or

- 5 (4) one or more potassium channel openers. Suitable potassium channel openers for use herein include nicorandil, cromokalim, levcromakalim, lemakalim, pinacidil, cliazoxide, minoxidil, charybdotoxin, glyburide, 4-amini pyridine, BaCl₂ ; and/or
- 10 (5) one or more dopaminergic agents, preferably apomorphine or a selective D2, D3 or D2/D3 agonist such as pramipexol and ropirinol (as claimed in WO 0023056), L-Dopa or carbi dopa, PNU 95666 (as claimed in WO 00 40226); and/or
- (6) one or more vasodilator agents. Suitable vasodilator agents for use herein include nimodopine, pinacidil, cyclandelate, isoxsuprine, chloroprumazine, halo peridol, Rec 15/2739, trazodone; and/or
- (7) one or more thromboxane A2 agonists; and/or
- 15 (8) one or more ergot alkaloids; Suitable ergot alkaloids are described in US patent 6,037,346 issued on 14th March 2000 and include acetergamine, brazergoline, bromerguride, cianergoline, delorgotrile, disulergine, ergonovine maleate, ergotamine tartrate, etisulergine, lergotrile, lysergide, mesulergine, metergoline, metergotamine, nicergoline, pergolide, propisergide, 20 proterguride, terguride; and/or
- (9) one or more compounds which modulate the action of atrial natruretic factor (also known as atrial naturetic peptide), B and C type naturetic factors such as inhibitors or neutral endopeptidase; and/or
- 25 (10) one or more compounds which inhibit angiotensin-converting enzyme such as enapril, and one or more combined inhibitors of angiotensin-converting enzyme and neutral endopeptidase such as omapatrilat; and/or
- (11) one or more angiotensin receptor antagonists such as losartan; and/or
- (12) one or more substrates for NO-synthase, such as L-arginine; and/or

- (13) one or more calcium channel blockers such as amlodipine; and/or
- (14) one or more antagonists of endothelin receptors and inhibitors or endothelin-converting enzyme; and/or
- (15) one or more cholesterol lowering agents such as statins (e.g. atorvastatin /
5 Lipitor - trade mark) and fibrates; and/or
- (16) one or more antiplatelet and antithrombotic agents, e.g. tPA, uPA, warfarin, hirudin and other thrombin inhibitors, heparin, thromboplastin activating factor inhibitors; and/or
- (17) one or more insulin sensitising agents such as rezulin and hypoglycaemic
10 agents such as glipizide; and/or
- (18) one or more COX 2 inhibitors; and/or
- (19) pregabalene; and/or
- (20) gabapentene; and/or
- (21) one or more acetylcholinesterase inhibitors such as donezipil; and/or
- 15 (22) one or more steroidal anti-inflammatory agents; and/or
- (23) one or more estrogen agonists and/or estrogen antagonists, preferably raloxifene or lasofoxifene, (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol and pharmaceutically acceptable salts thereof (compound A below) the preparation of which is detailed in WO
20 96/21656.



Compound A

5

(24) one or more one or more of a further PDE inhibitor, more particularly a PDE 2, 4, 7 or 8 inhibitor, preferably PDE2 inhibitor, said inhibitors preferably having an IC₅₀ against the respective enzyme of less than 100nM: and/or

10 (25) one or more of an NPY (neuropeptide Y) inhibitor, more particularly NPY1 or NPY5 inhibitor, preferably NPY1 inhibitor, preferably said NPY inhibitors (including NPY Y1 and NPY Y5) having an IC₅₀ of less than 100nM, more preferably less than 50nM, suitable NPY and in particular NPY1 inhibitor compounds are described in EP-A-1097718; and/or

15

(26) one or more of vasoactive intestinal peptide (VIP), VIP mimetic, more particularly mediated by one or more of the VIP receptor subtypes VPAC1, VPAC or PACAP (pituitary adenylate cyclase activating peptide), one or more of a VIP receptor agonist or a VIP analogue (eg Ro-125-1553) or a
20 VIP fragment, one or more of a α -adrenoceptor antagonist with VIP combination (eg Invicorp, Aviptadil); and/or

- (27) one or more of a melanocortin receptor agonist or modulator or melanocortin enhancer, such as melanotan II, PT-14, PT-141 or compounds claimed in WO-09964002, WO-00074679, WO-09955679, WO-00105401, WO-00058361, WO-00114879, WO-00113112, WO-09954358; and/or
- 5 (28) one or more of a serotonin receptor agonist, antagonist or modulator, more particularly agonists, antagonists or modulators for 5HT_{1A} (including VML 670), 5HT_{2A}, 5HT_{2C}, 5HT₃ and/or 5HT₆ receptors, including those described in WO-09902159, WO-00002550 and/or WO-00028993; and/or
- 10 (29) one or more of a modulator of transporters for noradrenaline, dopamine and/or serotonin, such as bupropion, GW-320659; and/or
- (30) one or more of a purinergic receptor agonist and/or modulator; and/or
- 15 (31) one or more of a neurokinin (NK) receptor antagonist, including those described in WO-09964008; and/or
- (32) one or more of an opioid receptor agonist, antagonist or modulator, preferably agonists for the ORL-1 receptor; and/or
- 20 (33) one or more of an agonist or modulator for oxytocin/vasopressin receptors, preferably a selective oxytocin agonist or modulator; and/or
- 25 (34) one or more modulators of cannabinoid receptors; and/or
- (35) one or more of an NEP inhibitor, preferably wherein said NEP is EC 3.4.24.11 and more preferably wherein said NEP inhibitor is a selective inhibitor for EC 3.4.24.11, more preferably a selective NEP inhibitor is a selective inhibitor for EC 3.4.24.11, which has an IC₅₀ of less than 100nM (e.g. omapatrilat, sampatrilat) suitable NEP inhibitor compounds are described in EP-A-1097719; and/or
- 30

- (36) one or more compounds which inhibit angiotensin-converting enzyme such as enalapril, and one or more combined inhibitors of angiotensin-converting enzyme and neutral endopeptidase such as omapatrilat; and/or
- 5 (37) one or more tricyclic antidepressants, e.g. amitriptyline; and/or
- (38) one or more non-steroidal anti-inflammatory agents; and/or
- (39) one or more angiotensin-converting enzyme (ACE) inhibitors, e.g.
10 quinapril; and/or
- (40) one or more anti-depressants (such as clomipramine and SSRIs (such as paroxetine and sertaline).

15

wherein said combination can be in the form of co-administration, simultaneous administration, concurrent administration, or stepwise administration.

20

Medical Use

The compounds of the invention are useful because they possess pharmacological activity in animals, especially mammals, including humans.

5 They are therefore indicated as pharmaceuticals, as well as for use as animal medicaments.

According to a further aspect of the invention there is provided the compounds of the invention for use as pharmaceuticals, and for use as animal medicaments.

10

In particular, compounds of the invention have been found to be potent and selective inhibitors of cGMP PDEs, such as cGMP PDE5, for example as demonstrated in the tests described below, and are thus useful in the treatment of medical conditions in humans, and in animals, in which cGMP PDEs, such as
15 cGMP PDE5, are indicated, and in which inhibition of cGMP PDEs, such as cGMP PDE5, is desirable.

By the term "treatment", we include both therapeutic (curative), palliative or prophylactic treatment.

20

Thus, according to a further aspect of the invention there is provided the use of the compounds of the invention in the manufacture of a medicament for the treatment of a medical condition in which a cGMP PDE (e.g. cGMP PDE5) is indicated. There is further provided the use of the compounds of the invention in
25 the manufacture of a medicament for the treatment of a medical condition in which inhibition of a cGMP PDE (e.g. cGMP PDE5) is desirable.

The compounds of the invention are thus expected to be useful for the curative, palliative or prophylactic treatment of mammalian sexual disorders. In particular,
30 the compounds are of value in the treatment of mammalian sexual dysfunctions such as male erectile dysfunction (MED), impotence, female sexual dysfunction (FSD), clitoral dysfunction, female hypoactive sexual desire disorder, female sexual arousal disorder, female sexual pain disorder or female sexual orgasmic

dysfunction (FSOD) as well as sexual dysfunction due to spinal cord injury or selective serotonin re-uptake inhibitor (SSRI) induced sexual dysfunction but, clearly, will be useful also for treating other medical conditions for which a potent and selective cGMP PDE5 inhibitor is indicated. Such conditions include

5 premature labour, dysmenorrhoea, benign prostatic hyperplasia (BPH), bladder outlet obstruction, incontinence, stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency, e.g. post-percutaneous transluminal coronary

10 angioplasty (post-PTCA), peripheral vascular disease, stroke, nitrate induced tolerance, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, diseases and conditions of the eye such as glaucoma, optic neuropathy, macular degeneration, elevated intra-ocular pressure, retinal or arterial occlusion and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome

15 (IBS).

Further medical conditions for which a potent and selective cGMP PDE5 inhibitor is indicated, and for which treatment with compounds of the present invention may be useful, include pre-eclampsia, Kawasaki's syndrome, nitrate tolerance,

20 multiple sclerosis, diabetic nephropathy, neuropathy including autonomic and peripheral neuropathy and in particular diabetic neuropathy and symptoms thereof (e.g. gastroparesis), peripheral diabetic neuropathy, Alzheimer's disease, acute respiratory failure, psoriasis, skin necrosis, cancer, metastasis, baldness, nutcracker oesophagus, anal fissure, haemorrhoids, hypoxic vasoconstriction, ,

25 hypoxic vasoconstriction, diabetes, type 2 diabetes mellitus, the insulin resistance syndrome, insulin resistance, impaired glucose tolerance, as well as the stabilisation of blood pressure during haemodialysis.

Particularly preferred conditions include MED and FSD.

30

Thus, the invention provides a method of treating or preventing a medical condition for which a cGMP PDE5 inhibitor is indicated, in an animal (e.g. a mammal, including a human being), which comprises administering a

therapeutically effective amount of a compound of the invention to a mammal in need of such treatment.

Pharmaceutical Preparations

5

The compounds will normally be administered orally or by any parenteral route, in the form of pharmaceutical preparations comprising the active ingredient, optionally in the form of a non-toxic organic, or inorganic, acid, or base, addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated, as well as the route of administration, the compositions may be administered at varying doses.

The compounds may also be combined with any other drugs useful in the inhibition of cGMP-PDEs, such as cGMP-PDE5.

15

The compounds, their pharmaceutically acceptable salts, and pharmaceutically acceptable solvates of either entity can be administered alone but, in human therapy will generally be administered in admixture with a suitable pharmaceutical excipient diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the compounds or salts or solvates thereof can be administered orally, buccally or sublingually in the form of tablets, capsules (including soft gel capsules), ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, or controlled-release such as sustained-, dual-, or pulsatile delivery applications. The compounds may also be administered via intracavernosal injection. The compounds may also be administered via fast dispersing or fast dissolving dosages forms.

Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine and starch (preferably corn, potato or tapioca starch), disintegrants such as sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation

binders such as polyvinylpyrrolidone, hydroxypropylmethyl cellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

5

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of the invention may be combined
10 with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

Modified release and pulsatile release dosage forms may contain
15 excipients such as those detailed for immediate release dosage forms together with additional excipients that act as release rate modifiers, these being coated on and/or included in the body of the device. Release rate modifiers include, but are not exclusively limited to, hydroxypropylmethyl cellulose, methyl cellulose, sodium carboxymethylcellulose, ethyl cellulose, cellulose acetate, polyethylene
20 oxide, Xanthan gum, Carbomer, ammonio methacrylate copolymer, hydrogenated castor oil, carnauba wax, paraffin wax, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, methacrylic acid copolymer and mixtures thereof. Modified release and pulsatile release dosage forms may contain one or a combination of release rate modifying excipients. Release rate
25 modifying excipients may be present both within the dosage form i.e. within the matrix, and/or on the dosage form i.e. upon the surface or coating.

Fast dispersing or dissolving dosage formulations (FDDFs) may contain the following ingredients: aspartame, acesulfame potassium, citric acid,
30 croscarmellose sodium, crospovidone, diascorbic acid, ethyl acrylate, ethyl cellulose, gelatin, hydroxypropylmethyl cellulose, magnesium stearate, mannitol, methyl methacrylate, mint flavouring, polyethylene glycol, fumed silica, silicon dioxide, sodium starch glycolate, sodium stearyl fumarate, sorbitol, xylitol. The

terms dispersing or dissolving as used herein to describe FDDFs are dependent upon the solubility of the drug substance used i.e. where the drug substance is insoluble a fast dispersing dosage form can be prepared and where the drug substance is soluble a fast dissolving dosage form can be prepared.

5

The compounds can also be administered parenterally, for example, intracavernosally, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion techniques. For such
10 parenteral administration they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily
15 accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

For oral and parenteral administration to human patients, the daily dosage level of the compounds or salts or solvates thereof will usually be from 10 to 500 mg
20 (in single or divided doses).

Thus, for example, tablets or capsules of the compounds or salts or solvates thereof may contain from 5mg to 250 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will
25 determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention. The skilled person will also appreciate
30 that, in the treatment of certain conditions (including MED. and FSD), compounds may be taken as a single dose on an "as required" basis (i.e. as needed or desired).

Example Tablet Formulation

In general a tablet formulation could typically contain between about 0.01mg and
5 500mg of the compound (or a salt thereof) whilst tablet fill weights may range
from 50mg to 1000mg. An example formulation for a 10mg tablet is illustrated:

	<u>Ingredient</u>	<u>%w/w</u>
	"Active" Compound	10.000*
10	Lactose	64.125
	Starch	21.375
	Croscarmellose Sodium	3.000
	Magnesium Stearate	1.500

15 * This quantity is typically adjusted in accordance with drug activity.

Such tablets can be manufactured by standard processes, for example, direct
compression or a wet or dry granulation process. The tablet cores may be
coated with appropriate overcoats.

20

The compounds can also be administered intranasally or by inhalation and are
conveniently delivered in the form of a dry powder inhaler or an aerosol spray
presentation from a pressurised container, pump, spray or nebuliser with the use
of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane,
25 dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane
(HFA 134A [trade mark] or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade
mark])), carbon dioxide or other suitable gas. In the case of a pressurised
aerosol, the dosage unit may be determined by providing a valve to deliver a
metered amount. The pressurised container, pump, spray or nebuliser may
30 contain a solution or suspension of the active compound, e.g. using a mixture of
ethanol and the propellant as the solvent, which may additionally contain a
lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example,
from gelatin) for use in an inhaler or insufflator may be formulated to contain a

powder mix of the compound and a suitable powder base such as lactose or starch.

Aerosol or dry powder formulations are preferably arranged so that each metered
5 dose or "puff" contains from 1 to 50 mg of the compound for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 1 to 50 mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

10 The compounds may also be formulated for delivery via an atomiser. Formulations for atomiser devices may contain the following ingredients as solubilisers, emulsifiers or suspending agents: water, ethanol, glycerol, propylene glycol, low molecular weight polyethylene glycols, sodium chloride, fluorocarbons, polyethylene glycol ethers, sorbitan trioleate, oleic acid.

15

Alternatively, the compounds or salts or solvates thereof can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The compounds or salts or solvates thereof may also be dermally administered. The
20 compounds or salts or solvates thereof may also be transdermally administered, for example, by the use of a skin patch. They may also be administered by the ocular, pulmonary or rectal routes.

For ophthalmic use, the compounds can be formulated as micronised
25 suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

30 For application topically to the skin, the compounds or salts or solvates thereof can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol,

polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl
5 esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility,
10 dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used
15 and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

Generally, in humans, oral administration of the compounds is the preferred route, being the most convenient and, for example in MED, avoiding the well-
20 known disadvantages associated with intracavernosal (i.c.) administration. A preferred oral dosing regimen in MED for a typical man is from 25 to 250 mg of compound when required. In circumstances where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, the drug may be administered parenterally, sublingually or
25 buccally.

For veterinary use, the compound, or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate or pro-drug thereof, is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the
30 veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular animal.

Thus, according to a further aspect there is provided a pharmaceutical formulation including a compound as detailed hereinbefore in admixture with a pharmaceutically or veterinarily acceptable adjuvant, diluent or carrier.

- 5 In addition to the fact that the compounds inhibit cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs) and in particular, are potent and selective inhibitors of cGMP PDE5, the compounds may also have the advantage that they may be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects
10 than, be more easily absorbed than, or they may have other useful pharmacological properties over, compounds known in the prior art.

BIOAVAILABILITY

- 15 Preferably the compounds of the invention are orally bioavailable. Oral bioavailability refers to the proportion of an orally administered drug that reaches the systemic circulation. The factors that determine oral bioavailability of a drug are dissolution, membrane permeability and metabolic stability. Typically, a screening cascade of firstly *in vitro* and then *in vivo* techniques is used to
20 determine oral bioavailability.

- Dissolution, the solubilisation of the drug by the aqueous contents of the gastrointestinal tract (GIT), can be predicted from *in vitro* solubility experiments conducted at appropriate pH to mimic the GIT. Preferably the compounds of the
25 invention have a minimum solubility of 50 mcg/ml. Solubility can be determined by standard procedures known in the art such as described in Adv. Drug Deliv. Rev. 23, 3-25, 1997.

- Membrane permeability refers to the passage of the compound through the cells
30 of the GIT. Lipophilicity is a key property in predicting this and is defined by *in vitro* Log $D_{7.4}$ measurements using organic solvents and buffer. Preferably the compounds of the invention have a Log $D_{7.4}$ of -2 to +4, more preferably -1 to +2. The log D can be determined by standard procedures known in the art such as

described in J. Pharm. Pharmacol. 1990, 42:144.

- Cell monolayer assays such as CaCo₂ add substantially to prediction of favourable membrane permeability in the presence of efflux transporters such as p-glycoprotein, so-called caco-2 flux. Preferably, compounds of the invention have a caco-2 flux of greater than $2 \times 10^{-6} \text{cms}^{-1}$, more preferably greater than $5 \times 10^{-6} \text{cms}^{-1}$. The caco flux value can be determined by standard procedures known in the art such as described in J. Pharm. Sci, 1990, 79, 595-600
- 10 Metabolic stability addresses the ability of the GIT or the liver to metabolise compounds during the absorption process: the first pass effect. Assay systems such as microsomes, hepatocytes etc are predictive of metabolic liability. Preferably the compounds of the Examples show metabolic stability in the assay system that is commensurate with an hepatic extraction of less than 0.5.
- 15 Examples of assay systems and data manipulation are described in Curr. Opin. Drug Disc. Devel., 201, 4, 36-44, Drug Met. Disp., 2000, 28, 1518-1523

Because of the interplay of the above processes further support that a drug will be orally bioavailable in humans can be gained by *in vivo* experiments in animals.

- 20 Absolute bioavailability is determined in these studies by administering the compound separately or in mixtures by the oral route. For absolute determinations (% absorbed) the intravenous route is also employed. Examples of the assessment of oral bioavailability in animals can be found in Drug Met. Disp., 2001, 29, 82-87; J. Med Chem, 1997, 40, 827-829, Drug Met. Disp., 1999, 25 27, 221-226

The biological activities of the compounds were determined by the following test methods.

30

Phosphodiesterase (PDE) inhibitory activity

The compounds of the present invention are potent and selective cGMP PDE5 inhibitors. *In vitro* PDE inhibitory activities against cyclic guanosine 3',5'-monophosphate (cGMP) and cyclic adenosine 3',5'-monophosphate (cAMP) phosphodiesterases were determined by measurement of their IC₅₀ values (the
5 concentration of compound required for 50% inhibition of enzyme activity).

The required PDE enzymes were isolated from a variety of sources, including human corpus cavernosum, human platelets, human cardiac ventricle, human skeletal muscle and human and canine retina, essentially by the method of W.J.
10 Thompson and M.M. Appleman (Biochem., 1971, 10, 311). In particular, the cGMP-specific PDE (PDE5) and the cGMP-inhibited cAMP PDE (PDE3) were obtained from human corpus cavernosum tissue or human platelets; the cGMP-stimulated PDE (PDE2) was obtained from human corpus cavernosum or human platelets; the calcium/calmodulin (Ca/CAM)-dependent PDE (PDE1) from human
15 cardiac ventricle; the cAMP-specific PDE (PDE4) from recombinant clone or human skeletal muscle; and the photoreceptor PDE (PDE6) from canine or human retina. Phosphodiesterases 7-11 were generated from full length human recombinant clones transfected into SF9 cells.

20 Assays were performed either using a modification of the "batch" method of W.J. Thompson et al. (Biochem., 1979, 18, 5228) or using a scintillation proximity assay for the direct detection of AMP/GMP using a modification of the protocol described by Amersham plc under product code TRKQ7090/7100. In summary, the effect of PDE inhibitors was investigated by assaying a fixed amount of
25 enzyme in the presence of varying inhibitor concentrations and low substrate, (cGMP or cAMP in a 3:1 ratio unlabelled to [³H]-labeled at a conc ~1/2 *K_m*) such that IC₅₀ \cong *K_i*. The final assay volume was made up to 102 μ l with assay buffer [20 mM Tris-HCl pH 7.4, 5 mM MgCl₂, 1 mg/ml bovine serum albumin]. Reactions were initiated with enzyme, incubated for 30-60 min at 30°C to give
30 <30% substrate turnover and terminated with 50 μ l yttrium silicate SPA beads (containing 3 mM of the respective unlabelled cyclic nucleotide for PDEs 3, 9 and 11). Plates were re-sealed and shaken for 20 min, after which the beads were allowed to settle for 30 min in the dark and then counted on a TopCount plate

reader (Packard, Meriden, CT). Radioactivity units were converted to % activity of an uninhibited control (100%), plotted against inhibitor concentration and inhibitor IC_{50} values obtained using the 'Fit Curve' Microsoft Excel extension or in-house equivalent. Results from these tests show that the compounds of the present
5 invention are potent and selective inhibitors of cGMP-specific PDE5.

Preferred compounds of formula (I) herein have IC_{50} values of less than or equal to about 30nM for the PDE5 enzyme. A more preferred group of compounds have IC_{50} values of less than or equal to about 10nM for the PDE5 enzyme. An
10 additional group of compounds having IC_{50} values of less than about 5nM for the PDE5 enzyme are further preferred.

Especially preferred herein are compounds which have an IC_{50} value of less than about 10, more preferably less than about 5 nM for the PDE5 enzyme in
15 combination with greater than 10-fold selectivity for the PDE5 enzyme versus the PDE6 enzyme. Highly preferred are compounds having IC_{50} values of less than about 10, more preferably less than about 5 nM for the PDE5 enzyme in combination with greater than 20-fold, preferably greater than 30-fold and especially greater than 40-fold selectivity for the PDE5 enzyme versus the PDE6
20 enzyme.

Functional activity

25

This was assessed in vitro by determining the capacity of a compound of the invention to enhance sodium nitroprusside-induced relaxation of pre-contracted rabbit corpus cavernosum tissue strips, as described by S.A. Ballard et al. (Brit. J. Pharmacol., 1996, 118 (suppl.), abstract 153P).

30

In vivo activity

In vivo activity is tested by screening test compounds in anaesthetised dogs to determine their capacity, after i.v. administration, to enhance the pressure rises in the corpora cavernosa of the penis induced by intracavernosal injection of sodium nitroprusside, using a method based on that described by Trigo-Rocha et al. (Neurourol. and Urodyn., 1994, 13, 71).

Safety Profile

The compounds may be tested at varying i.v and p.o. doses in animals such as mouse and dog, observing for any untoward effects.

Biological Activity

Table 1 illustrates the *in vitro* cGMP PDE5 inhibitory activities for a range of compounds of the invention.

TABLE 1

Example	PDE5 IC ₅₀ (nM)	PDE6 IC ₅₀ (nM)
13	11.9	609
2	13.8	592
3	23.0	922
12	1.8	163
6	2.2	85
10	3.2	152

Examples and Preparations

The synthesis of the compounds of general formula (I) and of the intermediates for use therein can be achieved by analogy with the processes of the Examples and Preparations hereinafter.

¹H nuclear magnetic resonance (NMR) spectra were recorded using either a Varian Unity 300 or a Varian Inova 400 spectrometer and were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

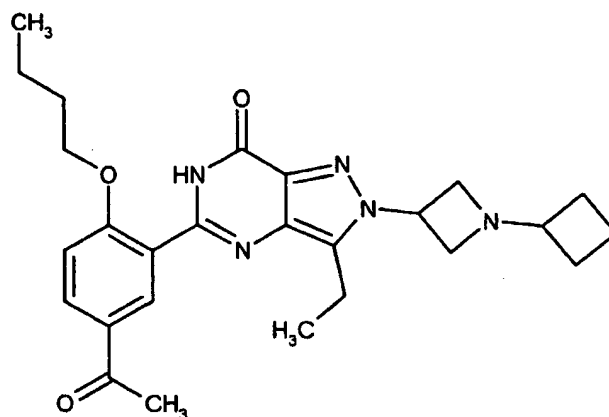
Mass spectra (m/z) were recorded using a Fisons Instruments Trio mass spectrometer in the thermospray ionisation mode (TSP) or using a Finnigan navigator in electrospray ionisation mode (ES) - positive and/or negative ionisation mode.

As used herein, the term "column chromatography" refers to normal phase chromatography using silica gel (0.04-0.06 mm).

Room temperature includes 20 to 25°C.

Example 1

5-(5-Acetyl-2-butoxyphenyl)-2-(1-cyclobutyl-3-azetidiny)-3-ethyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



A solution of the azetidine from preparation 14 (500mg, 0.785mmol) and cyclobutanone (176 μ l, 2.36mmol) in dichloromethane (4ml) was stirred at room temperature for 10 minutes, then sodium triacetoxymethylborohydride (419mg, 1.86mmol) added, and the reaction mixture stirred at room temperature for 3 hours. The mixture was diluted with dichloromethane (25ml) and washed with

water and sodium bicarbonate solution. The combined aqueous solutions were extracted with dichloromethane (2x25ml), and the combined organic solutions then washed with brine, dried (MgSO₄) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol (97.5:2.5) as eluant to give an oil. This was crystallised from diethyl ether, to afford the title compound as a white solid, 210mg.

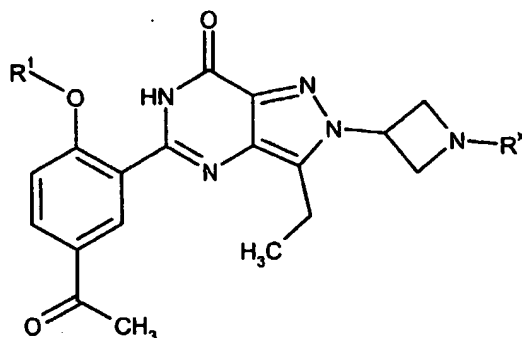
¹H NMR (CDCl₃, 400MHz) δ : 1.00 (t, 3H), 1.38 (t, 3H), 1.57 (m, 2H), 1.66-1.99 (m, 6H), 2.04 (m, 2H), 2.62 (s, 3H), 3.02 (q, 2H), 3.34 (m, 1H), 3.80 (d, 4H), 4.25 (t, 2H), 5.16 (m, 1H), 7.11 (d, 1H), 8.06 (dd, 1H), 8.95 (d, 1H), 10.54 (s, 1H).

LRMS : m/z (TSP⁺) 464.2 [MH⁺]

Microanalysis found: C, 66.88; H, 7.30; N, 14.85. C₂₆H₃₃N₅O₃·0.05H₂O requires C, 67.23; H, 7.18; N, 15.08%.

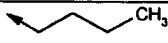
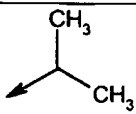
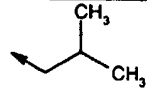
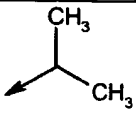
Examples 2 to 4

The following compounds of general formula:



were prepared from the appropriate azetidine compounds (preparations 14 and 15) and ketones, following similar procedures to that described in example 1.

Ex	R ³	R ^x	Yield (%)	Data
2			50 white solid	¹ H NMR (CDCl ₃ , 400MHz) δ : 1.08 (d, 6H), 1.36 (t, 3H), 1.63-1.92 (m, 4H), 2.01 (m, 2H), 2.26 (m, 1H), 2.60 (s,

				<p>3H), 3.00 (q, 2H), 3.30 (m, 1H), 3.79 (d, 4H), 4.00 (d, 2H), 5.15 (m, 1H), 7.05 (d, 1H), 8.02 (d, 1H), 8.88 (s, 1H), 10.48 (s, 1H).</p> <p>LRMS : m/z (TSP⁺) 464.2 [MH⁺]</p> <p>Microanalysis found: C, 66.24; H, 7.34; N, 14.43. C₂₆H₃₃N₅O₃·0.5H₂O requires C, 66.08; H, 7.25; N, 14.82%.</p>
3 ¹			18 white solid	<p>¹H NMR (CDCl₃, 400MHz) δ: 1.01 (m, 9H), 1.39 (t, 3H), 1.58 (m, 2H), 1.98 (m, 2H), 2.62 (m, 4H), 3.02 (q, 2H), 3.78 (dd, 2H), 3.92 (dd, 2H), 4.28 (t, 2H), 5.15 (m, 1H), 7.10 (d, 1H), 8.08 (dd, 1H), 8.98 (d, 1H), 10.55 (s, 1H).</p> <p>LRMS : m/z (TSP⁺) 452.2 [MH⁺]</p> <p>Microanalysis found: C, 65.97; H, 7.37; N, 15.36. C₂₅H₃₃N₅O₃·0.25H₂O requires C, 65.84; H, 7.40; N, 15.36%.</p>
4 ¹			38 white solid	<p>¹H NMR (CDCl₃, 400MHz) δ: 1.00 (d, 6H), 1.10 (d, 6H), 1.38 (t, 3H), 2.30 (m, 1H), 2.61 (m, 4H), 3.01 (q, 2H), 3.78 (dd, 2H), 3.90 (dd, 2H), 4.02 (d, 2H), 5.15 (m, 1H), 7.09 (d, 1H), 8.05 (dd, 1H), 8.94 (d, 1H), 10.50 (s, 1H).</p> <p>LRMS : m/z 452.1 [MH⁺]</p> <p>Microanalysis found: C, 65.32; H, 7.36; N, 14.92. C₂₆H₃₃N₅O₃·0.5H₂O requires C, 66.08; H, 7.25; N, 14.82%.</p>

1= 2 eq of triethylamine were also used in the reaction

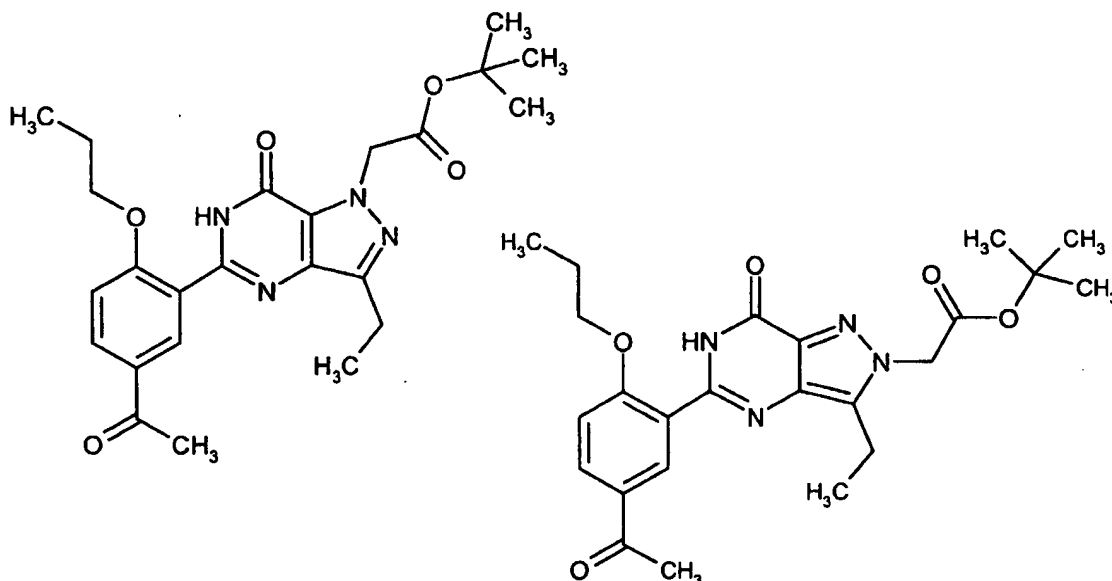
Example 5

tert-Butyl-5-[(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-1-yl]-acetate

and

5 Example 6

tert-Butyl-5-[(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl]-acetate



10

tert-Butyl bromoacetate (295 μ l, 2mmol) was added to a suspension of cesium carbonate (652mg, 2mmol) and the pyrazole from preparation 17 (680mg, 2mmol) in *N,N*-dimethylformamide (15ml) at room temperature, and the reaction was stirred for 18 hours. The mixture was quenched with water and extracted with diethyl ether (5x30ml) and ethyl acetate (3x20ml). The diethyl ether extracts were dried over Na₂SO₄, concentrated under reduced pressure and purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (95:5:0.5) and the product was recrystallised from dichloromethane/diisopropylether to afford the title compound of example 5 as a white solid, 171mg.

20

¹H NMR (CDCl₃, 400MHz) δ : 1.19 (t, 3H), 1.47 (m, 12H), 2.03 (m, 2H), 2.68 (s, 3H), 3.06 (q, 2H), 4.26 (t, 2H), 5.24 (s, 2H), 7.14 (d, 1H), 8.13 (d, 1H), 9.07 (s, 1H), 10.92 (br s, 1H).

LRMS : m/z (TSP⁺) 455.7 [MH⁺].

Microanalysis found: C, 63.29; H, 6.66; N, 12.24. C₂₄H₃₀N₄O₅ requires C, 63.42; H, 6.65; N, 12.33%.

- 5 The ethyl acetate extracts were dried over Na₂SO₄, concentrated under reduced pressure and purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (95:5:0.5) as eluant and the product was recrystallised from dichloromethane/diisopropylether to afford the title compound of example 6 as a white solid, 112mg.

- 10 ¹H NMR (CDCl₃, 400MHz) δ: 1.17 (t, 3H), 1.46 (m, 12H), 2.02 (m, 2H), 2.66 (s, 3H), 3.01 (q, 2H), 4.24 (t, 2H), 5.03 (s, 2H), 7.14 (d, 1H), 8.09 (d, 1H), 8.99 (s, 1H), 10.60 (br s, 1H).

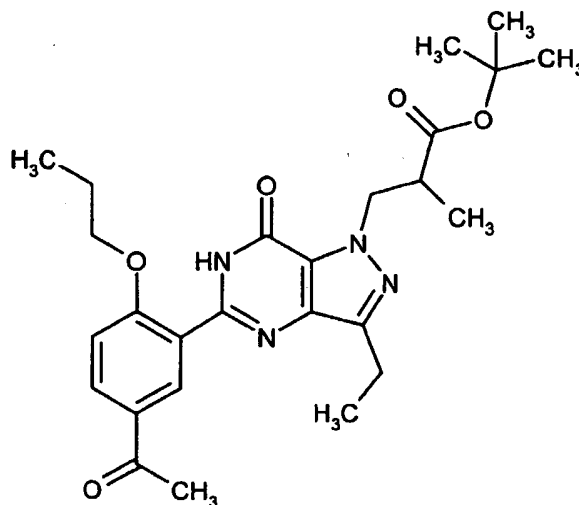
LRMS : m/z (TSP⁺) 455.4 [MH⁺].

Microanalysis found: C, 62.96; H, 6.65; N, 12.21. C₂₄H₃₀N₄O₅ requires C, 63.42;

- 15 H, 6.65; N, 12.33%.

Example 7

tert-Butyl-3-[(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-1-yl]-2-methylpropanoate



20

2-Bromo-*tert*-butylisobutyrate (446mg, 2mmol) was added to a suspension of cesium carbonate (652mg, 2mmol) and the pyrazole from preparation 17 (680mg, 2mmol) in N,N-dimethylformamide (15ml) at room temperature, and the

reaction was stirred for 18 hours. Starting material remained by TLC analysis, so the reaction was heated to 60°C for 36 hours, cooled to room temperature and quenched with water (50ml). The mixture was extracted with diethyl ether (3x50ml) and the combined organic extracts were dried over Na₂SO₄, concentrated under reduced pressure and purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (95:5:0.5) as eluant and the product was recrystallised from diisopropylether to afford the title compound as a white solid, 55mg.

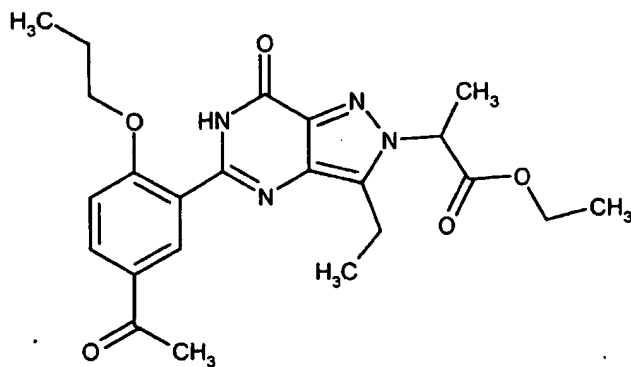
¹H NMR (CDCl₃, 300MHz) δ: 1.17 (m, 6H), 1.44 (m, 12H), 2.02 (m, 2H), 2.66 (s, 3H), 3.12 (q, 2H), 3.38 (m, 1H), 4.22 (m, 3H), 4.60 (dd, 1H), 7.13 (d, 1H), 8.08 (d, 1H), 9.00 (s, 1H), 10.60 (br s, 1H).

LRMS : m/z (TSP⁺) 483.3 [MH⁺].

Microanalysis found: C, 64.44; H, 7.09; N, 11.63. C₂₆H₃₄N₄O₅ requires C, 64.70; H, 7.10; N, 11.61%.

Example 8

Ethyl 2-[5-(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl]propanoate



Ethyl-2-bromopropanoate (362mg, 2mmol) was added to a suspension of cesium carbonate (652mg, 2mmol) and the pyrazole from preparation 17 (680mg, 2mmol) in N,N-dimethylformamide (15ml) at room temperature, and the reaction was stirred at 60°C for 13 hours, cooled to room temperature and quenched with water (50ml). The mixture was extracted with diethyl ether (3x50ml) and ethyl acetate (3x50ml) and the combined organic extracts were dried over Na₂SO₄, concentrated under reduced pressure and purified by column chromatography on

silica gel using dichloromethane:methanol:0.88 ammonia (97.5:2.5:0.25) as eluant. This gave two products, the most polar of which was crystallised from diisopropylether to afford the title compound as a white solid, 98mg.

¹H NMR (CDCl₃, 300MHz) δ: 1.13 (t, 3H), 1.23 (t, 3H), 1.43 (t, 3H), 2.00 (m, 5H),
5 2.65 (s, 3H), 3.05 (q, 2H), 4.21 (m, 4H), 5.21 (m, 1H), 7.10 (d, 1H), 8.08 (d, 1H),
8.98 (s, 1H), 10.55 (br s, 1H).

LRMS : m/z (ESP⁺) 441 [MH⁺], 463 [MNa⁺].

Microanalysis found: C, 62.53; H, 6.39; N, 12.66. C₂₃H₂₈N₄O₅ requires C, 62.71; H, 6.41; N, 12.66%.

10

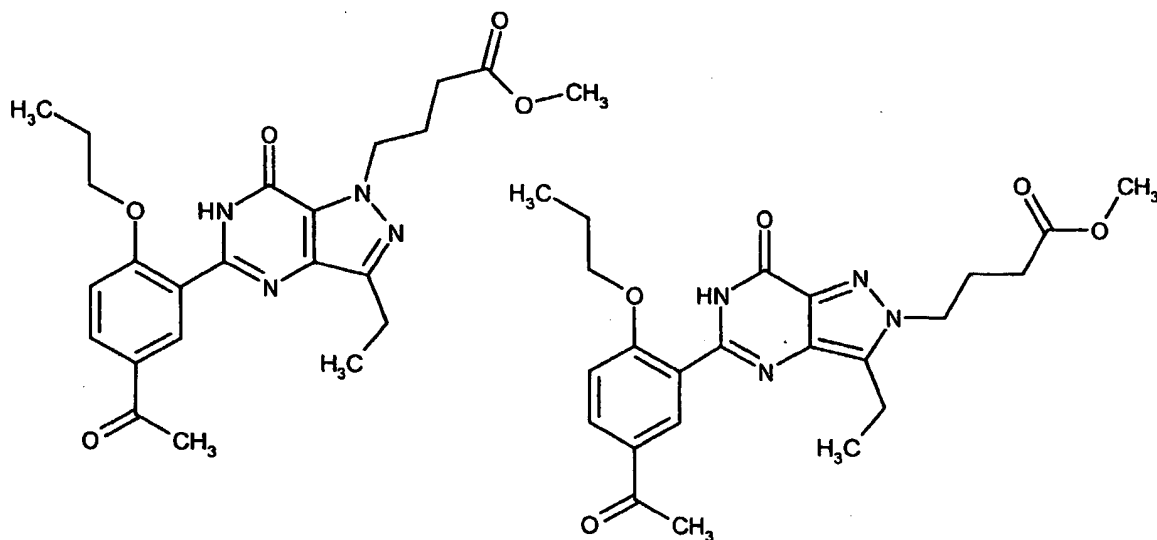
Example 9

Methyl-4-[5-(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-1H-
pyrazolo[4,3-d]pyrimidin-1-yl]-butanoate
and

15

Example 10

Methyl-4-[5-(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-
pyrazolo[4,3-d]pyrimidin-1-yl]-butanoate



20

Methyl 4-bromobutanoate (370mg, 2mmol) was added to a suspension of cesium carbonate (652mg, 2mmol) and the pyrazole from preparation 17 (680mg, 2mmol) in N,N-dimethylformamide (15ml) at room temperature, and the reaction was stirred for 64 hours. The mixture was quenched with water and extracted

with diethyl ether (4x20ml) and ethyl acetate (2x20ml). The ethyl acetate extracts were washed with water (2x20ml), brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (97.5:2.5:0.25) and the least polar fraction was collected and recrystallised twice from acetonitrile to afford the title compound of example 9 as a white solid, 31mg.

¹H NMR (CDCl₃, 400MHz) δ: 1.19 (t, 3H), 1.43 (t, 3H), 2.04 (m, 2H), 2.28 (m, 2H), 2.39 (m, 2H), 2.66 (s, 3H), 3.01 (q, 2H), 3.65 (s, 3H), 4.27 (t, 2H), 4.66 (t, 2H), 7.15 (d, 1H), 8.14 (d, 1H), 9.08 (s, 1H), 10.91 (br s, 1H).

LRMS : m/z (ESP⁺) 441 [MH⁺], 439 [MH].

Microanalysis found: C, 62.21; H, 6.45; N, 12.51. C₂₃H₂₈N₄O₅. 0.2mol H₂O requires C, 62.21; H, 6.45; N, 12.62%.

The other fractions were combined and re-chromatographed eluting with pentane:isopropyl alcohol:0.88 ammonia (80:20:1.5). This gave two major products, the most polar of which was triturated with diisopropylether to afford the title compound of example 10 as a white solid, 12.4mg.

¹H NMR (CDCl₃, 300MHz) δ: 1.16 (t, 3H), 1.45 (t, 3H), 2.01 (m, 2H), 2.34 (m, 2H), 2.42 (m, 2H), 2.66 (s, 3H), 3.06 (q, 2H), 3.70 (s, 3H), 4.24 (t, 2H), 4.40 (t, 2H), 7.13 (d, 1H), 8.10 (d, 1H), 8.99 (s, 1H), 10.59 (br s, 1H).

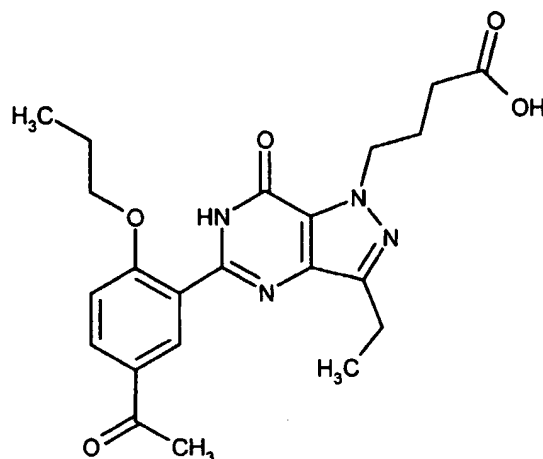
LRMS : m/z (ESP⁺) 441 [MH⁺], 463 [MNa⁺], 439 [MH].

Microanalysis found: C, 62.24; H, 6.37; N, 12.57. C₂₃H₂₈N₄O₅ requires C, 62.71; H, 6.41; N, 12.72%.

25

Example 11

4-[5-(5-Acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-1-yl]butanoic acid



1N Sodium hydroxide solution (1ml, 1mmol) was added to a solution of the ester from example 9 (30mg, 0.07mmol) in dioxan (1ml) and the reaction was stirred at room temperature for 2.5 hours. The reaction was adjusted to pH 2 with 2N hydrochloric acid, stirred for 30 min and the resulting precipitate was filtered and washed with water. The product was dried *in vacuo* to afford the title compound as a white solid, 13mg.

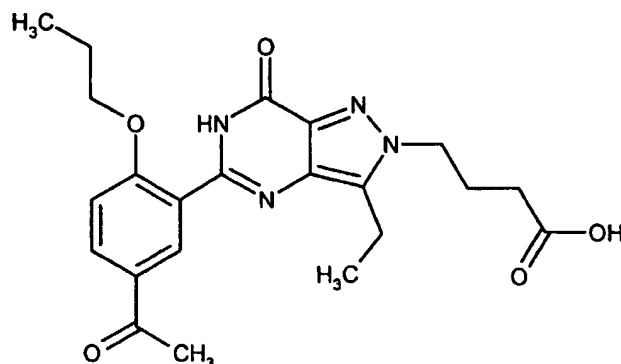
^1H NMR (CDCl_3 , 400MHz) δ : 1.18 (t, 3H), 1.43 (t, 3H), 2.04 (m, 2H), 2.30 (m, 2H), 2.41 (m, 2H), 2.68 (s, 3H), 3.02 (q, 2H), 4.27 (t, 2H), 4.72 (t, 2H), 7.13 (d, 1H), 8.12 (d, 1H), 9.02 (s, 1H), 11.06 (br s, 1H).

LRMS : m/z (ESP^+) 427 [MH^+], 449 [MNa^+], 425 [MH].

Microanalysis found: C, 61.45; H, 6.16; N, 12.92. $\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_5$. 0.2mol H_2O requires C, 61.44; H, 6.19; N, 13.03%.

Example 12

4-[5-(5-Acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl]butanoic acid



1N Sodium hydroxide solution (1ml, 1mmol) was added to a solution of the ester from example 10 (25mg, 0.06mmol) in dioxan (1ml) and the reaction was stirred at room temperature for 3 hours. The reaction was adjusted to pH 2 with 2N hydrochloric acid, diluted with water (5ml) and half of the solvent was removed under reduced pressure. The resulting precipitate was filtered, washed with water, dried *in vacuo* and slurried with acetonitrile. The slurry was then filtered and the solid was dried *in vacuo* to afford the title compound as a white solid, 13mg.

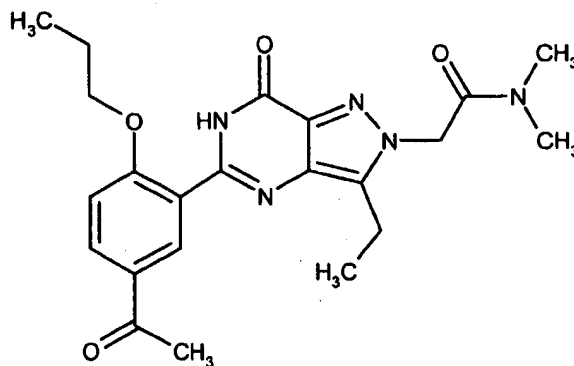
^1H NMR (CDCl_3 , 300MHz) δ : 1.15 (t, 3H), 1.45 (t, 3H), 2.01 (m, 2H), 2.35 (m, 2H), 2.49 (m, 2H), 2.67 (s, 3H), 3.09 (q, 2H), 4.26 (t, 2H), 4.42 (t, 2H), 7.13 (d, 1H), 8.11 (d, 1H), 8.95 (s, 1H), 10.73 (br s, 1H).

LRMS : m/z (ESP^+) 427 [MH^+], 449 [MNa^+]

Microanalysis found: C, 61.41; H, 6.12; N, 12.85. $\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_5 \cdot 0.2\text{mol H}_2\text{O}$ requires C, 61.44; H, 6.19; N, 13.03%.

Example 13

2-[5-(5-Acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl]-N,N-dimethylacetamide



2-Chloro-N,N-dimethylacetamide (178mg, 1.47mmol) was added to a suspension of cesium carbonate (480mg, 1.47mmol) and the pyrazole from preparation 17 (500mg, 1.47mmol) in N,N-dimethylformamide (10ml) at room temperature, and the reaction was stirred for 84 hours. The mixture was quenched with water and stood at room temperature for 18 hours, and the resultant white solid was isolated by filtration and washed with water, before being dried *in vacuo*. The solid was purified by column chromatography on silica gel using

dichloromethane:methanol:0.88 ammonia (95:5:0.5) to give two products, the most polar of which was collected and crystallised from acetonitrile to afford the title compound as a white solid, 132mg.

¹H NMR (CDCl₃, 400MHz) δ: 1.15 (t, 3H), 1.47 (t, 3H), 2.00 (m, 2H), 2.64 (s, 3H),
5 3.05 (m, 5H), 3.18 (s, 3H), 4.23 (m, 2H), 5.20 (s, 2H), 7.11 (d, 1H), 8.10 (d, 1H),
8.98 (s, 1H), 11.04 (br s, 1H).

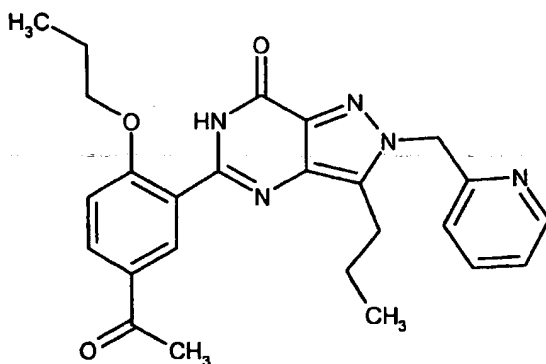
LRMS : m/z (ESP⁺) 426 [MH⁺], 448 [MNa⁺].

Microanalysis found: C, 61.95; H, 6.38; N, 16.55. C₂₂H₂₇N₅O₄ requires C, 61.95; H, 6.40; N, 16.46%.

10

Example 14

5-(5-Acetyl-2-propoxyphenyl)-3-propyl-2-(2-pyridinylmethyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one



15

Polyphosphoric acid (20g) and the pyrazole carboxamide from preparation 18 (1.3g, 2.8mmol) were heated to 190-200°C for 15 min and the reaction was cooled to room temperature. The mixture was quenched with water, basified to
20 pH 8 with sodium carbonate and extracted with dichloromethane (x2). The combined organic extracts were dried over Na₂SO₄, concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using dichloromethane:methanol (100:0 changing to 99:1 then 94:6) to afford the title compound as an off-white solid, 30mg.

25 ¹H NMR (CDCl₃, 400MHz) δ: 0.98 (t, 3H), 1.16 (t, 3H), 1.78 (m, 2H), 2.03 (m, 2H),
2.63 (s, 3H), 3.00 (t, 2H), 4.25 (t, 2H), 5.69 (s, 2H), 7.09 (m, 2H), 7.22 (m, 1H),
7.62 (t, 1H), 8.09 (d, 1H), 8.58 (d, 1H), 8.99 (s, 1H), 10.62 (br s, 1H).

LRMS : m/z (TSP⁺) 446.2 [MH⁺].

PREPARATION 1

5 **4-(2-n-Propoxybenzamido)-3-n-propyl-1H-pyrazole-5-carboxamide**

A solution of 2-n-propoxybenzoyl chloride (57.6 g, 0.291 mol) in dichloromethane (50 ml) was added dropwise to a stirred, ice-cooled suspension of 4-amino-3-propyl-1H-pyrazole-5-carboxamide (the compound of Preparation 8 of WO 98/49166) (35.0 g, 0.208 mol) in dry pyridine (350 ml) and the resulting mixture
10 stirred for 18 hours at room temperature, then evaporated under reduced pressure. The residue was azeotroped with toluene (2 x 100ml) and the resulting brown solid triturated with ether (100 ml) to give the title compound (83.0 g) as a beige solid.

δ (CH₃OH_{d4}): 0.92 (3H,t), 1.14 (3H,t), 1.65 (2H,m), 1.94 (2H,m), 2.80 (2H,t), 4.20
15 (2H,t), 7.08 (1H,m), 7.18 (1H,d), 7.52 (1H,m), 8.04 (1H,d). LRMS: m/z 331 (M+1)⁺.

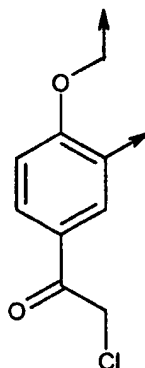
PREPARATION 2

20 **5-(2-n-Propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one**

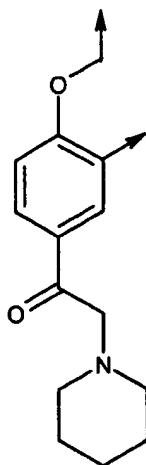
Potassium t-butoxide (93.0 g, 0.832 mol) was added portionwise to a stirred solution of the title compound of Preparation 1 (83.0 g, 0.25 mol) in propan-2-ol (800 ml) under nitrogen and the mixture heated for 18 hours under reflux, then
25 allowed to cool. Water (100 ml) was added, to produce a homogeneous solution which was acidified to pH 6 with 2M hydrochloric acid. The resulting white precipitate was collected and dried by suction to provide the title compound (37.4 g). Found: C, 65.36; H, 6.49; N, 17.99. C₁₇H₂₀N₄O₂ requires C, 65.37; H, 6.45; N, 17.94%. δ (CDCl₃): 1.05 (3H,t), 1.16 (3H,t), 2.00 (4H,m), 3.04 (2H,t), 4.20
30 (2H,t), 7.07 (1H,d), 7.16 (1H,m), 7.48 (1H,m), 8.52 (1H,d), 11.30 (1H,s), 12.25 (1H,s). LRMS: m/z 313 (M+1)⁺.

PREPARATION 3**2-Cyanomethyl-5-(2-n-propoxyphenyl)-3-n-propyl-****2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one**

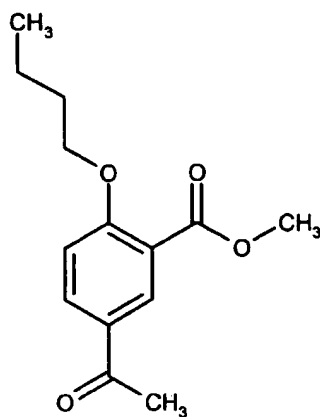
- 5 A 2M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (4.42 ml, 8.8 mmol) was added to a stirred, ice-cooled solution of the title compound of Preparation 2 (2.3 g, 7.4 mmol) in tetrahydrofuran (25 ml) and the resulting solution stirred for 30 minutes, before being cooled to about -70°C. Bromoacetonitrile (0.54 ml, 7.7 mmol) was added dropwise, the cooling bath
- 10 removed and, after a further 20 hours, the reaction mixture carefully quenched with methanol (5 ml) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol (99:1 to 95:5), followed by crystallisation from hexane:ethyl acetate, to afford the title compound (1.89 g) as a white solid.
- 15 Found: C, 64.84; H, 5.98; N, 19.71. $C_{19}H_{21}N_5O_2$ requires C, 64.94; H, 6.02; N, 19.93%. δ ($CDCl_3$): 1.12 (6H,m), 1.98 (4H,m), 3.08 (2H,t), 4.20 (2H,t), 5.26 (2H,s), 7.05 (1H,d), 7.16 (1H,m), 7.48 (1H,m), 8.42 (1H,d), 11.00 (1H,s). LRMS: m/z 703 ($2M+1$)⁺.
- 20 Haloketones of the structure illustrated may be prepared *via* Friedel-Crafts chemistry on intermediates such as the title compound of Preparation 3 such as in known in the art.



- 25 Reaction of this halo ketone with an amine provides compounds having R⁴ functionality as detailed hereinbefore.



5

*Preparation 4**Methyl 5-acetyl-2-butoxybenzoate*

n-Butyl iodide (13.2ml, 117mmol) was added to a mixture of methyl 5-acetylsalicylate (15g, 77mmol) and potassium carbonate (16g, 117mmol) in acetonitrile (500ml), and the reaction stirred at 60°C for 18 hours. TLC analysis showed starting material remaining, so additional n-butyl iodide (26.4ml, 234mmol) and potassium carbonate (16g, 117mmol) were added and the reaction stirred at 60°C for a further 72 hours. The cooled mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate and water. The phases were separated, the organic layer washed with brine, dried (MgSO₄) and evaporated under reduced pressure to afford the title compound as a yellow oil that crystallised on

drying *in vacuo*, 17.4g.

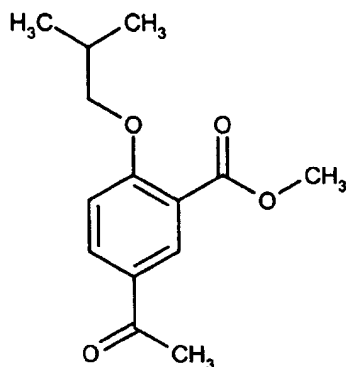
^1H NMR (CDCl_3 , 400MHz) : 0.99 (t, 3H), 1.54 (m, 2H), 1.82 (m, 2H), 2.58 (s, 3H), 3.90 (s, 3H), 4.11 (t, 2H), 7.00 (d, 1H), 8.06 (dd, 1H), 8.38 (d, 1H).

LRMS : m/z (TSP $^+$) 251.1 [MH $^+$]

5

Preparation 5

Methyl 5-acetyl-2-isobutoxybenzoate

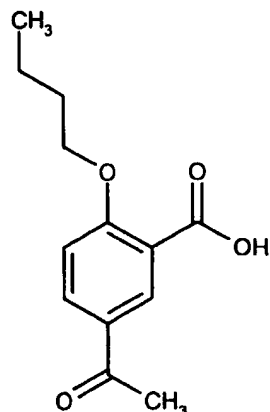


1-iodo-2-methylpropane (13.35ml, 117mmol) was added to a mixture of methyl 5-acetylsalicylate (15g, 77mmol) and potassium carbonate (16g, 117mmol) in acetonitrile (500ml), and the reaction stirred at 60°C for 18 hours. TLC analysis showed starting material remaining, so additional 1-iodo-2-methylpropane (26.7ml, 234mmol) and potassium carbonate (16g, 117mmol) were added and the reaction stirred at 60°C for a further 72 hours. TLC analysis showed starting material still remaining, so additional 1-iodo-2-methylpropane (13.35ml, 117mmol) and potassium carbonate (16g, 117mmol) were added and the reaction stirred at reflux for a further 3 hours. The cooled mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate and 1N sodium hydroxide solution. The phases were separated, the aqueous extracted with further ethyl acetate, and the combined organic solutions washed with brine, dried (MgSO_4) and evaporated under reduced pressure to give the title compound as a brown oil, 8.3g.

^1H NMR (CDCl_3 , 400MHz) : 1.05 (d, 6H), 2.16 (m, 1H), 2.58 (s, 3H), 3.85 (d, 2H), 3.90 (s, 3H), 6.99 (d, 1H), 8.08 (dd, 1H), 8.39 (d, 1H).

LRMS : m/z (TSP $^+$) 251.2 [MH $^+$]

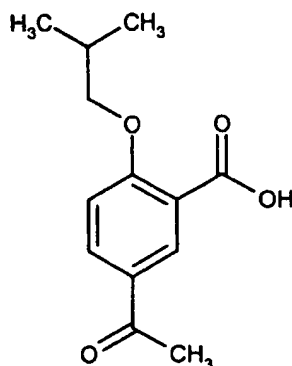
25

Preparation 6**5-Acetyl-2-butoxybenzoic acid**

- 5 Sodium hydroxide pellets (5.6g, 139mmol) were added to a solution of the ester from preparation 4 (17.4g, 70mmol) in dioxan (400ml) and water (40ml), and the reaction stirred at room temperature for 18 hours. The mixture was concentrated under reduced pressure, the residue acidified to pH 1 using 2N hydrochloric acid, and the aqueous extracted with dichloromethane (250ml, 3x100ml). The
- 10 combined organic solutions were washed with brine, dried (MgSO₄) and evaporated under reduced pressure to give the title compound as an orange solid, 15.16g.

¹H NMR (CDCl₃, 400MHz) : 1.02 (t, 3H), 1.57 (m, 2H), 1.96 (m, 2H), 2.60 (s, 3H), 4.35 (t, 2H), 7.12 (d, 1H), 8.20 (d, 1H), 8.74 (s, 1H).

- 15 LRMS : m/z (TSP⁺) 237.1 [MH⁺]

Preparation 7**5-Acetyl-2-isobutoxybenzoic acid**

- 20 The title compound was obtained in 83% yield from the ester from

preparation 5, following the procedure described in preparation 6.

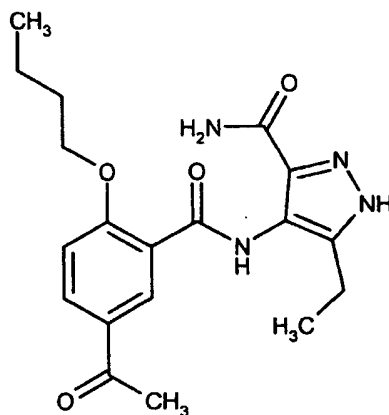
^1H NMR (CDCl_3 , 400MHz) : 1.14 (d, 6H), 2.25 (m, 1H), 2.61 (s, 3H), 4.10 (d, 2H), 7.13 (d, 1H), 8.20 (d, 1H), 8.77 (s, 1H).

LRMS : m/z (TSP $^+$) 254.2 [MNH_4^+]

5

Preparation 8

4-[(5-Acetyl-2-butoxybenzoyl)amino]-5-ethyl-1H-pyrazole-3-carboxamide



Oxalyl chloride (16.8ml, 193mmol) was added to an ice-cooled solution of the
10 acid from preparation 6 (15.16g, 64mmol) in N,N-dimethylformamide (0.5ml) and
dichloromethane (300ml). Once addition was complete, the solution was allowed
to warm to room temperature, and stirred for 1.5 hours. The solution was
concentrated under reduced pressure and azeotroped with dichloromethane (2x),
then dried *in vacuo*. This intermediate acid chloride was dissolved in
15 dichloromethane (100ml), triethylamine (27ml, 193mmol) added, followed by a
solution of 4-amino-3-ethyl-1H-pyrazole-5-carboxamide (WO 9849166) (9.9g,
64mmol) in dichloromethane (200ml), and the reaction stirred at room
temperature for 3 hours. The mixture was washed with sodium bicarbonate
solution, this aqueous solution re-extracted with dichloromethane (4x100ml), and
20 the combined organic extracts dried (MgSO_4) and evaporated under reduced
pressure. The residual brown solid was triturated with ethyl acetate, the solid
filtered, washed with diethyl ether and dried. This solid was further purified by
column chromatography on silica gel using dichloromethane:methanol:0.88
ammonia (95:5:0.5) to afford the title compound as a beige solid, 20.12g.

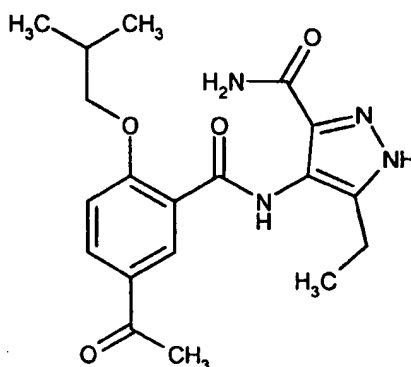
^1H NMR (CDCl_3 , 400MHz) : 0.98 (t, 3H), 1.28 (t, 3H), 1.50 (m, 2H), 1.98 (m, 2H), 2.60 (s, 3H), 2.97 (q, 2H), 4.35 (t, 2H), 5.38 (br s, 1H), 6.78 (br s, 1H), 7.08 (d, 1H), 8.15 (dd, 1H), 8.81 (d, 1H), 10.38 (br s, 1H).

LRMS : m/z (TSP^+) 373.0 [MH^+]

- 5 Microanalysis found: C, 60.85; H, 6.58; N, 14.73. $\text{C}_{19}\text{H}_{24}\text{N}_4\text{O}_4$ requires C, 61.28; H, 6.50; N, 15.04%.

Preparation 9

4-[5-Acetyl-2-isobutoxybenzoyl]amino]-5-ethyl-1H-pyrazole-3-carboxamide



10

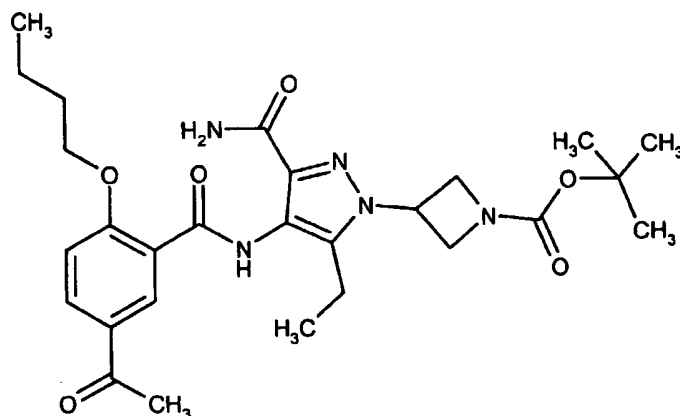
The title compound was obtained as a beige solid in 86% yield from the acid from preparation 7 and 4-amino-3-ethyl-1H-pyrazole-5-carboxamide (WO 9849166), following a similar procedure to that described in preparation 8.

- ^1H NMR (CDCl_3 , 400MHz) : 1.02 (d, 6H), 1.25 (t, 3H), 2.38 (m, 1H), 2.60 (s, 3H), 2.96 (q, 2H), 4.06 (d, 2H), 5.33 (br s, 1H), 6.78 (br s, 1H), 7.08 (d, 1H), 8.15 (d, 1H), 8.80 (s, 1H), 10.22 (s, 1H).

LRMS : m/z (ES^+) 395 [MNa^+]

Preparation 10

- 20 tert-Butyl 3-[4-[(5-acetyl-2-butoxybenzoyl)amino]-3-(aminocarbonyl)-5-ethyl-1H-pyrazol-1-yl]-1-azetidinecarboxylate



Cesium carbonate (19.7g, 60.0mmol) was added to a mixture of the pyrazole carboxamide from preparation 8 (15g, 40mmol) and *tert*-butyl-3-iodo-1-azetidinecarboxylate (EP 992493) (17.4g, 60.0mmol) in N,N-dimethylformamide (200ml) and the reaction stirred at 50°C for 16 hours. TLC analysis showed starting material remaining, so additional *tert*-butyl-3-iodo-1-azetidinecarboxylate (EP 992493) (6.0g, 18.4mmol) was added and the reaction stirred for a further 18 hours. The mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate and sodium bicarbonate solution. The resulting solid was filtered off, washed with ether and dried to give the title compound as a white solid, 6.8g.

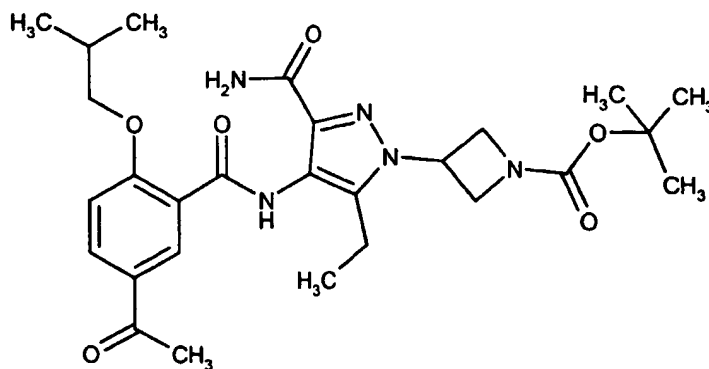
The filtrate was separated, the organic layer washed with brine, dried (MgSO₄) and evaporated under reduced pressure to give a brown solid. This was triturated with ethyl acetate and warm diethyl ether, filtered and dried *in vacuo*, to afford additional product as a white solid, 8.2g, (15.0g in total).

¹H NMR (DMSO-d₆, 400MHz) : 0.88 (t, 3H), 1.06 (t, 3H), 1.40 (m, 11H), 1.82 (m, 2H), 2.54 (s, 3H), 2.70 (m, 2H), 4.26 (m, 6H), 5.32 (m, 1H), 7.32 (m, 2H), 7.50 (br s, 1H), 8.08 (d, 1H), 8.42 (s, 1H), 10.00 (s, 1H).

LRMS : m/z (TSP⁺) 528.1 [MH⁺]

Preparation 11

tert-Butyl 3-[4-[(5-acetyl-2-isobutoxybenzoyl)amino]-3-(aminocarbonyl)-5-ethyl-1H-pyrazol-1-yl]-1-azetidinecarboxylate



Cesium carbonate (11.4g, 35mmol) was added to a mixture of the pyrazole from preparation 9 (8.7g, 23mmol) and *tert*-butyl-3-iodo-1-azetidinecarboxylate (EP 992493) (19.9g, 35mmol) in *N,N*-dimethylformamide (100ml) and the reaction stirred at 50°C for 16 hours. The cooled mixture was concentrated under reduced pressure and the residue partitioned between water (250ml)/saturated sodium bicarbonate solution (200ml) and ethyl acetate (100ml). The layers were separated, and the aqueous solution extracted with ethyl acetate (4x100ml). The combined organic layers were washed with brine, dried (MgSO₄) and evaporated under reduced pressure to give a brown solid. This was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (100:0:0 to 97.5:2.5:0.25) to afford the title compound as a white solid, after trituration from ethyl acetate, 6.33g.

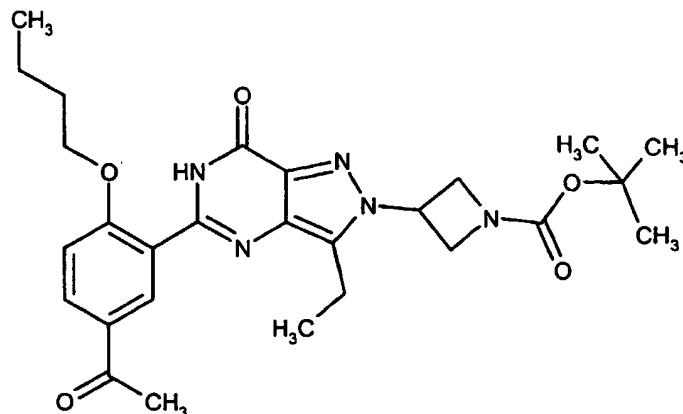
¹H NMR (CDCl₃, 400MHz) : 1.02 (d, 6H), 1.18 (t, 3H), 1.46 (s, 9H), 2.38 (m, 1H), 2.60 (s, 3H), 2.85 (q, 2H), 4.05 (d, 2H), 4.37 (m, 2H), 4.44 (m, 2H), 5.08 (m, 1H), 5.28 (br s, 1H), 6.74 (br s, 1H), 7.06 (d, 1H), 8.14 (dd, 1H), 8.78 (d, 1H), 10.17 (s, 1H).

LRMS : m/z (TSP⁺) 528.2 [MH⁺]

20

Preparation 12

tert-Butyl 3-[5-(5-acetyl-2-butoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl]-1-azetidinecarboxylate

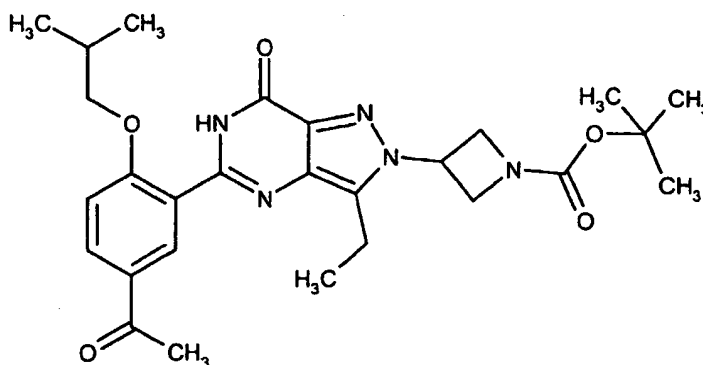


- Cesium carbonate (26.8g, 83mmol) was added to a mixture of the compound from preparation 10 (14.5g, 28mmol), molecular sieves, and n-butyl acetate (3.6ml, 28mmol) in n-butanol (150ml) and the reaction stirred at 140°C for 10 hours. The cooled mixture was concentrated under reduced pressure, the brown residue partitioned between ethyl acetate and sodium bicarbonate solution, (some sonication required), then filtered. The filtrate was separated, the aqueous layer further extracted with ethyl acetate (4x), and the combined organic solutions washed with brine, dried (MgSO₄) and evaporated under reduced pressure, to give the title compound, 8.3g.

¹H NMR (CDCl₃, 400MHz) : 1.02 (t, 3H), 1.38 (t, 3H), 1.46 (s, 9H), 1.58 (m, 2H), 1.98 (m, 2H), 2.62 (s, 3H), 3.03 (q, 2H), 4.30 (m, 2H), 4.39 (m, 2H), 4.65 (bm, 2H), 5.23 (m, 1H), 7.11 (d, 1H), 8.06 (dd, 1H), 8.98 (d, 1H), 10.60 (s, 1H).

15 Preparation 13

tert-Butyl 3-[5-(5-acetyl-2-iso-butoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl]-1-azetidinecarboxylate



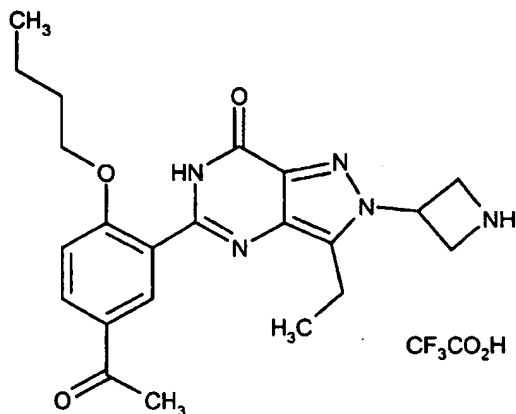
The title compound was obtained in 90% yield as an orange foam, from the compound from preparation 11, iso-butanol and iso-butyl acetate, following a similar procedure to that described in preparation 12.

¹H NMR (CDCl₃, 400MHz) : 1.08 (d, 6H), 1.37 (t, 3H), 1.42 (s, 9H), 2.25 (m, 1H), 2.60 (s, 3H), 3.00 (q, 2H), 4.00 (d, 2H), 4.37 (m, 2H), 4.63 (bm, 2H), 5.22 (m, 1H), 7.05 (d, 1H), 8.03 (dd, 1H), 8.90 (d, 1H), 10.52 (s, 1H).

LRMS : m/z (TSP⁺) 410.1 [M-Boc]⁺

Preparation 14

10 5-(5-Acetyl-2-butoxyphenyl)-2-(3-azetidinyl)-3-ethyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one trifluoroacetate



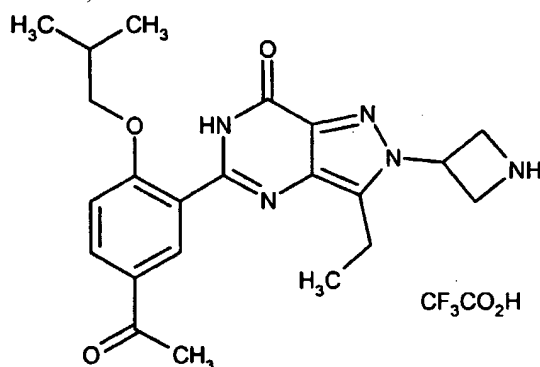
Trifluoroacetic acid (4.3ml) was added to a solution of the protected azetidine from preparation 12 (2.84g, 5.58mmol) in dichloromethane (15ml), and the reaction stirred at room temperature for 1.5 hours. The solution was evaporated under reduced pressure, and the residual brown gum triturated from dichloromethane (20ml) and diethyl ether (150ml). The resulting solid was filtered, washed with further diethyl ether and dried *in vacuo*, to afford the title compound as a beige solid, 3.06g.

20 ¹H NMR (CD₃OD, 400MHz) : 0.97 (t, 3H), 1.32 (t, 3H), 1.50 (m, 2H), 1.82 (m, 2H), 2.60 (s, 3H), 3.03 (q, 2H), 4.22 (t, 2H), 4.65 (m, 4H), 5.72 (m, 1H), 7.25 (d, 1H), 8.18 (d, 1H), 8.41 (s, 1H).

LRMS : m/z (TSP⁺) 410.1 [MH⁺]

Preparation 15

5-(5-Acetyl-2-isobutoxyphenyl)-2-(3-azetidinyl)-3-ethyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one trifluoroacetate



5

The title compound was obtained as a beige solid, from the protected azetidine from preparation 13, following a similar procedure to that described in preparation 14.

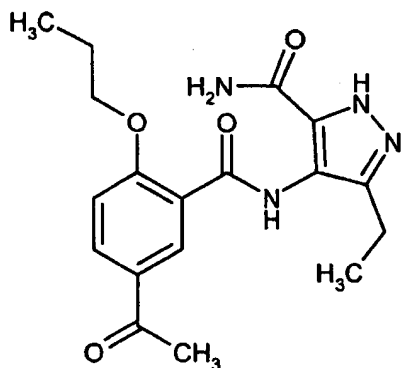
¹H NMR (CD₃OD, 400MHz) : 1.01 (d, 6H), 1.30 (t, 3H), 2.1.0 (m, 1H), 2.60 (s, 3H), 3.05 (q, 2H), 4.00 (d, 2H), 4.65 (m, 4H), 5.72 (m, 1H), 7.25 (d, 1H), 8.18 (dd, 1H), 8.38 (d, 1H).

10

LRMS : m/z (TSP⁺) 410.1 [MH⁺]

Preparation 16

15 4-[(5-Acetyl-2-propoxybenzoyl)amino]-5-ethyl-1H-pyrazole-3-carboxamide



Oxalyl chloride (5.45ml, 46.4mmol) was added to a solution of 5-acetyl-2-*n*-propoxy-benzoic acid (WO 9312095) (11.1g, 30.9mmol) in N,N-dimethylformamide (0.1ml) and dichloromethane (200ml) under nitrogen at room

20

temperature. Once addition was complete the solution was stirred for 1 hour. The solution was concentrated under reduced pressure and azeotroped with toluene, and the intermediate acid chloride was dissolved in dichloromethane (200ml). Triethylamine (10.4ml, 46.4mmol) was added followed by 4-amino-3-ethyl-1H-pyrazole-5-carboxamide (WO 9849166) (7.7g, 30.9mmol) and the reaction was stirred at room temperature for 16 hours. The mixture was washed with 1N hydrochloric acid (2x100ml), 10% sodium bicarbonate solution (100ml) and brine (100ml), dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was recrystallised from acetonitrile to afford the title compound as a crystalline solid, 14.8g.

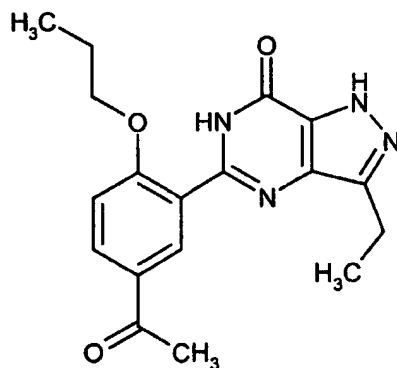
¹H NMR (CDCl₃, 400MHz) : 1.06 (t, 3H), 1.27 (t, 3H), 2.03 (m, 2H), 2.62 (s, 3H), 2.95 (m, 2H), 4.29 (t, 2H), 5.43 (br s, 1H), 6.82 (br s, 1H), 7.10 (d, 1H), 8.16 (d, 1H), 8.84 (s, 1H), 10.39 (br s, 2H) .

LRMS : m/z (TSP⁺) 359.1 [MH⁺].

Microanalysis found: C, 60.04; H, 6.18; N, 15.79. C₁₈H₂₂N₄O₄ requires C, 60.27; H, 6.18; N, 15.62%.

Preparation 17

5-[(5-Acetyl-2-propoxyphenyl)-3-ethyl-1,6-dihydro-pyrazolo[4,3-d]pyrimidin-7-one

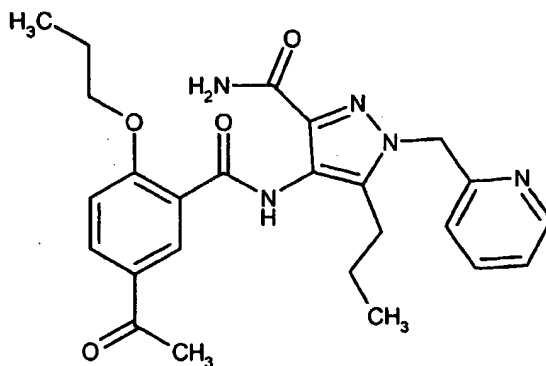


Potassium *tert*-butoxide (4.37g, 39mmol) was added to a solution of the pyrazole carboxamide from preparation 16 (14g, 39mmol) in n-propanol (120ml) and ethyl acetate (10ml) and the reaction was stirred at reflux for 24 hours. TLC analysis showed starting material remaining, so additional potassium *tert*-butoxide (4.37g, 39mmol) was added and the reaction was stirred at reflux for a further 18 hours.

- TLC analysis still showed starting material, so another addition of potassium *tert*-butoxide (4.37g, 39mmol) was made and the reaction was refluxed for a further 70 hours. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane and water. The organic layer was removed, washed with water (2x), brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (95:5:0.5) and the product was recrystallised from acetonitrile to afford the title compound as a white solid, 4.94g.
- 10 ¹H NMR (CDCl₃, 400MHz) : 1.18 (t, 3H), 1.50 (t, 3H), 2.03 (m, 2H), 2.67 (s, 3H), 3.11 (q, 2H), 4.28 (t, 2H), 7.15 (d, 1H), 8.14 (d, 1H), 9.08 (s, 1H), 11.59 (br s, 1H), 11.93 (br s, 1H).
- LRMS : m/z (TSP⁺) 341.3 [MH⁺].
- Microanalysis found: C, 63.18; H, 5.93; N, 12.22. C₁₈H₂₀N₄O₅ requires C, 63.51; H, 5.92; N, 16.46%.
- 15

Preparation 18

- 4-[(5-Acetyl-2-propoxybenzoyl)amino]-5-propyl-1-(pyridin-2-ylmethyl)-1H-pyrazole-3-carboxamide
- 20



- Oxalyl chloride (1.6ml, 18mmol) was added to an ice-cooled solution of 5-acetyl-2-*n*-propoxybenzoic acid (WO 9312095) (2g, 9mmol) in N,N-dimethylformamide (0.2ml) and dichloromethane (200ml) under nitrogen.. Once addition was complete the solution was allowed to warm to room temperature for 3 hours and the solvent was removed under reduced pressure. The intermediate acid chloride was dissolved in pyridine (50ml) and 4-amino-5-propyl-1-(pyridin-2-ylmethyl)-1H-
- 25

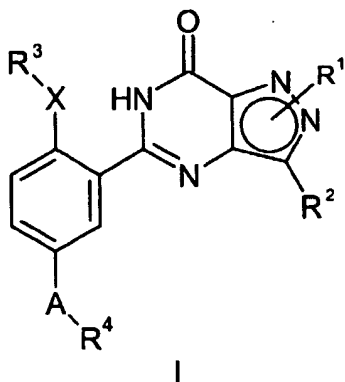
pyrazole-3-carboxamide (WO 9954333) (1.5g, 5.8mmol) and the reaction was stirred at reflux for 3 hours, then at room temperature for 18 hours. The mixture was partitioned between dilute sodium carbonate solution and dichloromethane, and the organic layer was dried over Na₂SO₄ and concentrated under reduced
5 pressure. The residue was purified by column chromatography on silica gel using dichloromethane:methanol (100:0 changing to 98:2 then 92:8) to afford the title compound as a beige solid, 1.5g.

¹H NMR (CDCl₃, 400MHz) : 0.81 (t, 3H), 1.06 (t, 3H), 1.46 (m, 2H), 2.03 (m, 2H), 2.61 (s, 3H), 2.87 (m, 2H), 4.29 (t, 2H), 5.36 (br s, 1H), 5.47 (s, 2H), 6.70 (br
10 s, 1H), 6.94 (d, 1H), 7.09 (d, 1H), 7.22 (m, 1H), 7.28 (m, 1H), 8.15 (d, 1H), 8.60 (m, 1H), 8.81 (s, 1H), 10.31 (br s, 1H).

LRMS : m/z (TSP⁺) 464.3 [MH⁺].

Claims

1. A compound of general formula I:



5

or pharmaceutically or veterinarily acceptable salts, solvates, polymorphs
or pro-drugs thereof wherein:

A represents C(O) or CH(OH);

10

X represents O or NR⁵;

15

R¹, R³, R⁴ and R⁵ independently represent H, C₁-C₆ alkyl, Het, C₁-C₆
alkylHet, aryl or C₁-C₆ alkylaryl (which latter five groups may all be
optionally substituted and/or terminated with one or more substituents
selected from halo, cyano, nitro, OR⁶, OC(O)R⁶, C(O)R⁶, C(O)OR⁶,
NR⁶C(O)NR⁷R⁸, NR⁶C(O)OR⁶, OC(O)NR⁷R⁸, C(O)NR⁹R¹⁰, NR⁹R¹⁰,
SO₂NR⁹R¹⁰, SO₂R¹¹, C₁-C₆ alkyl, Het, C₁-C₆ alkylHet, aryl or C₁-C₆
alkylaryl wherein said latter five substituent and/or terminal groups are all
optionally substituted and/or terminated with one or more substituents
selected from halo, cyano, nitro, OR¹², OC(O)R¹², C(O)R¹², C(O)OR¹²,
NR¹²C(O)NR¹³R¹⁴, NR¹²C(O)OR¹², OC(O)NR¹³R¹⁴, C(O)NR¹⁵R¹⁶, NR¹⁵R¹⁶,
SO₂NR¹⁵R¹⁶, SO₂R¹⁷); or when X represents NR⁵ then R³ and R⁵ together
with the nitrogen atom to which they are bound can form a heterocyclic
ring which is optionally substituted and/or terminated with one or more
substituents selected from halo, cyano, nitro, OR¹², OC(O)R¹², C(O)R¹²,

25

$C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$,
 $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17} ;

5 R^2 represents H, halo, cyano, nitro, OR^6 , $OC(O)R^6$, $C(O)R^6$, $C(O)OR^6$,
 $NR^6C(O)NR^7R^8$, $NR^6C(O)OR^6$, $OC(O)NR^7R^8$, $C(O)NR^9R^{10}$, NR^9R^{10} ,
 $SO_2NR^9R^{10}$, SO_2R^{11} , C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6
alkylaryl (which latter five groups may all be optionally substituted and/or
terminated with one or more substituents selected from halo, cyano, nitro,
 OR^6 , $OC(O)R^6$, $C(O)R^6$, $C(O)OR^6$, $NR^6C(O)NR^7R^8$, $NR^6C(O)OR^6$,
10 $OC(O)NR^7R^8$, $C(O)NR^9R^{10}$, NR^9R^{10} , $SO_2NR^9R^{10}$, SO_2R^{11} , C_1 - C_6 alkyl, Het,
 C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl wherein said latter five substituent
and/or terminal groups are all optionally substituted and/or terminated with
one or more substituents selected from halo, cyano, nitro, OR^{12} ,
 $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$,
15 $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17});

R^6 represents H, C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl
(which latter five groups are all optionally substituted and/or terminated
with one or more substituents selected from halo, cyano, nitro, OR^{12} ,
20 $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$,
 $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17});

R^7 and R^8 independently represent H, C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl
or C_1 - C_6 alkylaryl (which latter five groups are all optionally substituted
25 and/or terminated with one or more substituents selected from halo,
cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$,
 $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$,
 SO_2R^{17}); or R^7 and R^8 together with the nitrogen atom to which they are
bound can form a heterocyclic ring;

30 R^9 and R^{10} independently represent H, $C(O)R^6$, SO_2R^{11} , C_1 - C_6 alkyl, Het,
 C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl (which latter five groups are all
optionally substituted and/or terminated with one or more substituents

selected from halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17} ; or R^9 and R^{10} together with the nitrogen atom to which they are bound can form a heterocyclic ring;

5

wherein when R^7 and R^8 , or R^9 and R^{10} together with the nitrogen atom to which they are bound form a heterocyclic ring, said heterocyclic ring is optionally substituted and/or terminated with one or more substituents selected from: halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17} ;

10

R^{11} represents a C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl group is optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17} ;

15

R^{12} represents H or C_1 - C_6 alkyl;

20

R^{13} and R^{14} independently represent H or C_1 - C_6 alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are bound can form a heterocyclic ring;

25

R^{15} and R^{16} independently represent H, $C(O)R^{12}$, SO_2R^{17} or C_1 - C_6 alkyl; or R^{15} and R^{16} together with the nitrogen atom to which they are bound can form a heterocyclic ring;

R^{17} represents C_1 - C_6 alkyl;

30

Het represents an optionally substituted four- to twelve-membered heterocyclic group, which group contains one or more heteroatoms selected from nitrogen, oxygen, sulphur and mixtures thereof;

with the proviso that when X represents O and R^1 represents H, C_1 - C_3 alkyl optionally substituted with fluoro or C_3 - C_5 cycloalkyl then

5 R^2 does not represent H, C_1 - C_6 alkyl optionally substituted with one or more fluoro substituents or with C_3 - C_6 cycloalkyl; or

R^3 does not represent C_1 - C_6 alkyl optionally substituted with one or more fluoro substituents or with C_3 - C_6 cycloalkyl; C_3 - C_5 cycloalkyl; C_3 - C_6 alkenyl; or C_3 - C_6 alkynyl; or

10

R_4 does not represent C_1 - C_4 alkyl optionally substituted with OH, NR^9R^{10} , CN, $CONR^9R^{10}$, $SO_2NR^9R^{10}$ or CO_2R^6 wherein R^6 is H or C_1 - C_4 alkyl and R^9 and R^{10} are each independently H or C_1 - C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-substituted piperizinyll or imidazolyl group wherein said group is optionally substituted with C_1 - C_4 alkyl or OH; C_2 - C_4 alkenyl optionally substituted with CN, $CONR^9R^{10}$ or CO_2R^6 ; C_2 - C_4 alkanoyl optionally substituted with NR^9R^{10} ; $(C_2-C_4)OH$ optionally substituted with NR^9R^{10} ; $(C_2-C_3)alkoxy(C_1-C_2)alkyl$ optionally substituted with OH or NR^9R^{10} .

15

20

2. A compound as defined in Claim 1 wherein:

25 X represents O;

A represents C(O) or CH(OH);

R^1 represents C_1 - C_6 alkyl substituted and/or terminated with OR^6 , C(O) OR^6 , C(O) NR^9R^{10} or NR^9R^{10} wherein said latter four groups are optionally substituted and/or terminated as defined hereinbefore;

30

or

R^1 represents Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl optionally

substituted and/or terminated with one or more substituents selected from halo, C₁-C₆ alkyl, OR⁶, C(O)OR⁶, C(O)NR⁹R¹⁰ and NR⁹R¹⁰ wherein said latter five groups are optionally substituted and/or terminated as defined hereinbefore;

5

R² and R³ independently represent C₁-C₆ alkyl, Het, C₁-C₆ alkylHet, aryl or C₁-C₆ alkylaryl optionally substituted and/or terminated with one or more substituents selected from halo, OR⁶, C(O)OR⁶ and NR⁹R¹⁰ wherein said latter three groups are optionally substituted and/or terminated as defined hereinbefore;

10

R⁴ represents C₁-C₆ alkyl, Het, C₁-C₆ alkylHet, aryl or C₁-C₆ alkylaryl optionally substituted and/or terminated with one or more substituents selected from halo and OR⁶ wherein said OR⁶ group is optionally substituted and/or terminated as defined hereinbefore;

15

wherein R⁶, R⁹ and R¹⁰ are as hereinbefore defined.

3. A compound as defined in Claim 1 or 2 wherein:

20

A represents C(O) and X represents O;

R¹ represents C₁-C₆ alkyl optionally substituted and/or terminated with one or more substituent groups selected from OR⁶, C(O)OR⁶ and C(O)NR⁹R¹⁰;

25

or

R¹ represents Het or C₁-C₆ alkylHet optionally substituted and/or terminated with one or more substituent groups selected from C₁-C₆ alkyl, OR⁶, C(O)OR⁶ and C(O)NR⁹R¹⁰;

30

R² represents C₁-C₆ alkyl optionally substituted and/or terminated with one or more substituent groups selected from halo and OR⁶;

R³ represents C₁-C₆ alkyl optionally substituted and/or terminated with one or more substituents selected from halo and OR⁶;

5 R⁴ represents C₁-C₆ alkyl optionally substituted and/or terminated with one or more substituents selected from halo and OR⁶;

wherein R⁶, R⁹ and R¹⁰ are as hereinbefore defined.

4. A compound as defined in any of the preceding claims wherein:

10

A represents C(O) and X represents O;

15 R¹ represents C₁-C₄ alkyl, an azetidiny group substituted and/or terminated with one or more substituent groups selected from C₃-C₄ alkyl, OR⁶, C(O)OR⁶ and C(O)NR⁹R¹⁰;

or

20 R¹ represents a (C₁-C₆)pyridiny group which may be optionally substituted with one or more substituent groups selected from C₃-C₄ alkyl, OR⁶, C(O)OR⁶ and C(O)NR⁹R¹⁰;

R² represents C₁-C₃ alkyl optionally substituted and/or terminated with one or more substituent groups selected from halo and OR⁶;

25 R³ represents C₁-C₄ alkyl optionally substituted and/or terminated with one or more substituents selected from halo and OR⁶;

R⁴ represents C₁-C₃ alkyl optionally substituted and/or terminated with one or more substituents selected from halo and OR⁶;

30

wherein R^6 is H or a C_1 - C_4 alkyl group and wherein R^9 and R^{10} are independently selected from methyl or ethyl groups.

5. A compound according to any of the preceding claims wherein:

5

A represents $C(O)$ and X represents O;

R^1 represents C_2 - C_3 alkyl group substituted and/or terminated with one or more substituent groups selected from OR^6 or $C(O)OR^6$;

10

R^2 represents C_2 - C_3 alkyl, and is preferably ethyl, optionally substituted and/or terminated with one or more substituent groups selected from halo and OR^6 ;

15

R^3 represents C_3 - C_4 alkyl, and is preferably propyl, optionally substituted and/or terminated with one or more substituents selected from halo and OR^6 ;

20

R^4 represents C_1 - C_2 alkyl, and is preferably ethyl, optionally substituted and/or terminated with one or more substituents selected from halo and OR^6 ;

wherein R^6 is H or a C_2 - C_4 alkyl group.

- 25 6. Compound as defined in any of Claims 1 to 5 for use as a pharmaceutical or as an animal medicament.

7. A formulation comprising a compound as defined in any of Claims 1 to 5 in admixture with a pharmaceutically or veterinarily acceptable adjuvant, diluent or carrier.

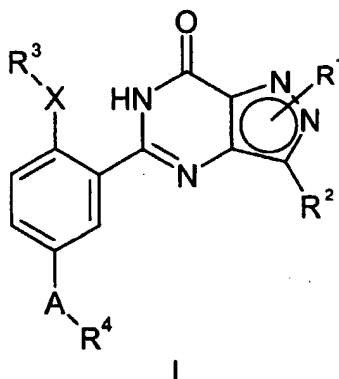
30

8. The use of a compound as defined in any of Claims 1 to 5 in the manufacture of a medicament for the curative or prophylactic treatment of a medical condition for which inhibition of cGMP PDE5 is desired.

5 9. Use as claimed in Claim 8 wherein the condition is male erectile dysfunction (MED), impotence, female sexual dysfunction (FSD), clitoral dysfunction, female hypoactive sexual desire disorder, female sexual arousal disorder, female sexual pain disorder or female sexual orgasmic dysfunction (FSOD) or a cardiovascular disorder.

10

10. The use of a compound of general formula I:



15 or pharmaceutically or veterinarily acceptable salts, solvates, polymorphs or pro-drugs thereof wherein:

A represents C(O) or CH(OH);

20 X represents O or NR⁵;

R¹, R³, R⁴ and R⁵ independently represent H, C₁-C₆ alkyl, Het, C₁-C₆ alkylHet, aryl or C₁-C₆ alkylaryl (which latter five groups may all be optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR⁶, OC(O)R⁶, C(O)R⁶, C(O)OR⁶, NR⁶C(O)NR⁷R⁸, NR⁶C(O)OR⁶, OC(O)NR⁷R⁸, C(O)NR⁹R¹⁰, NR⁹R¹⁰, SO₂NR⁹R¹⁰, SO₂R¹¹, C₁-C₆ alkyl, Het, C₁-C₆ alkylHet, aryl or C₁-C₆

25

alkylaryl wherein said latter five substituent and/or terminal groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17}); or when X represents NR^5 then R^3 and R^5 together with the nitrogen atom to which they are bound can form a heterocyclic ring which is optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17} ;

R^2 represents H, halo, cyano, nitro, OR^6 , $OC(O)R^6$, $C(O)R^6$, $C(O)OR^6$, $NR^6C(O)NR^7R^8$, $NR^6C(O)OR^6$, $OC(O)NR^7R^8$, $C(O)NR^9R^{10}$, NR^9R^{10} , $SO_2NR^9R^{10}$, SO_2R^{11} , C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl (which latter five groups may all be optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR^6 , $OC(O)R^6$, $C(O)R^6$, $C(O)OR^6$, $NR^6C(O)NR^7R^8$, $NR^6C(O)OR^6$, $OC(O)NR^7R^8$, $C(O)NR^9R^{10}$, NR^9R^{10} , $SO_2NR^9R^{10}$, SO_2R^{11} , C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl wherein said latter five substituent and/or terminal groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17});

R^6 represents H, C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl (which latter five groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17});

R^7 and R^8 independently represent H, C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl (which latter five groups are all optionally substituted and/or terminated with one or more substituents selected from halo,

cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17} ; or R^7 and R^8 together with the nitrogen atom to which they are bound can form a heterocyclic ring;

5

R^9 and R^{10} independently represent H, $C(O)R^6$, SO_2R^{11} , C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl (which latter five groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17}); or R^9 and R^{10} together with the nitrogen atom to which they are bound can form a heterocyclic ring;

10

wherein when R^7 and R^8 , or R^9 and R^{10} together with the nitrogen atom to which they are bound form a heterocyclic ring, said heterocyclic ring is optionally substituted and/or terminated with one or more substituents selected from: halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17} ;

15

20

R^{11} represents a C_1 - C_6 alkyl, Het, C_1 - C_6 alkylHet, aryl or C_1 - C_6 alkylaryl group is optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, OR^{12} , $OC(O)R^{12}$, $C(O)R^{12}$, $C(O)OR^{12}$, $NR^{12}C(O)NR^{13}R^{14}$, $NR^{12}C(O)OR^{12}$, $OC(O)NR^{13}R^{14}$, $C(O)NR^{15}R^{16}$, $NR^{15}R^{16}$, $SO_2NR^{15}R^{16}$, SO_2R^{17} ;

25

R^{12} represents H or C_1 - C_6 alkyl;

30

R^{13} and R^{14} independently represent H or C_1 - C_6 alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are bound can form a heterocyclic ring;

R^{15} and R^{16} independently represent H, $C(O)R^{12}$, SO_2R^{17} or C_1-C_6 alkyl; or R^{15} and R^{16} together with the nitrogen atom to which they are bound can form a heterocyclic ring;

5 R^{17} represents C_1-C_6 alkyl;

Het represents an optionally substituted four- to twelve-membered heterocyclic group, which group contains one or more heteroatoms selected from nitrogen, oxygen, sulphur and mixtures thereof in the
10 manufacture of a medicament for the curative or prophylactic treatment of a medical condition selected from premature labour, dysmenorrhoea, nitrate induced tolerance, pre-eclampsia, Kawasaki's syndrome, nitrate tolerance, multiple sclerosis, diabetic nephropathy, neuropathy including autonomic and peripheral neuropathy and in particular diabetic neuropathy
15 and symptoms thereof (e.g. gastroparesis), peripheral diabetic neuropathy, Alzheimer's disease, acute respiratory failure, psoriasis, skin necrosis, cancer, metastasis, baldness, nutcracker oesophagus, anal fissure, haemorrhoids, hypoxic vasoconstriction, , hypoxic vasoconstriction, diabetes, type 2 diabetes mellitus, the insulin resistance
20 syndrome, insulin resistance, impaired glucose tolerance, as well as the stabilisation of blood pressure during haemodialysis.

INTERNATIONAL SEARCH REPORT

In national Application No

F01/1B 02/00679

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/505 C07D487/04 A61P3/00 A61P15/00 A61P25/00
 //(C07D487/04,239:00,231:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 28902 A (PFIZER LTD ;PFIZER (US); PFIZER RES & DEV (IE); ELLIS PETER (GB);) 22 December 1994 (1994-12-22) Compounds (I) page 2, paragraph 3 ---	1-10
X	ESTRADE M ET AL: "EFFECT OF A CGMP-SPECIFIC PHOSPHODIESTERASE INHIBITOR ON RETINAL FUNCTION" EUROPEAN JOURNAL OF PHARMACOLOGY, AMSTERDAM, NL, vol. 352, no. 2/3, 1998, pages 157-163, XP000872495 ISSN: 0014-2999 compound GF248 abstract --- -/--	1-10

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

8 document member of the same patent family

Date of the actual completion of the international search

4 June 2002

Date of mailing of the international search report

11/06/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Fritz, M

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/IB 02/00679

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 526 004 A (PFIZER LTD ;PFIZER (US)) 3 February 1993 (1993-02-03) compounds (I); examples abstract -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 02/00679

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9428902	A	22-12-1994	AT 163852 T	15-03-1998
			AU 676571 B2	13-03-1997
			AU 6797394 A	03-01-1995
			CA 2163446 A1	22-12-1994
			CN 1124926 A ,B	19-06-1996
			CZ 9503242 A3	17-07-1996
			DE 69408981 D1	16-04-1998
			DE 69408981 T2	02-07-1998
			DK 702555 T3	06-04-1998
			WO 9428902 A1	22-12-1994
			EP 0702555 A1	27-03-1996
			ES 2113656 T3	01-05-1998
			FI 955911 A	08-12-1995
			GR 3026520 T3	31-07-1998
			IL 109873 A	27-12-1998
			IL 121836 A	27-12-1998
			JP 11286444 A	19-10-1999
			JP 11263728 A	28-09-1999
			JP 2925034 B2	26-07-1999
			JP 9503996 T	22-04-1997
			KR 262926 B1	01-09-2000
			LV 12269 A	20-05-1999
			LV 12269 B	20-08-1999
			NO 954757 A	24-11-1995
			NO 20000702 A	24-11-1995
			NO 20000703 A	24-11-1995
			NZ 266463 A	24-03-1997
			NZ 314110 A	23-02-2001
			PL 311948 A1	18-03-1996
			RU 2130776 C1	27-05-1999
			ZA 9404018 A	08-12-1995
EP 0526004	A	03-02-1993	AT 159019 T	15-10-1997
			AU 636816 B2	06-05-1993
			AU 1954592 A	11-03-1993
			BR 1100029 A3	06-06-2000
			BR 9202525 A	16-03-1993
			CA 2073226 A1	10-01-1993
			CN 1068329 A ,B	27-01-1993
			CZ 281316 B6	14-08-1996
			DE 69222595 D1	13-11-1997
			DE 69222595 T2	12-02-1998
			DK 526004 T3	03-11-1997
			EG 19978 A	31-10-1996
			EP 0526004 A1	03-02-1993
			ES 2107506 T3	01-12-1997
			FI 923157 A	10-01-1993
			FI 980420 A	24-02-1998
			GR 3025424 T3	27-02-1998
			HU 220046 B	28-10-2001
			HU 9500119 A3	28-06-1995
			IE 922222 A1	13-01-1993
			IL 102368 A	23-07-1996
			JP 2554824 B2	20-11-1996
			JP 5202050 A	10-08-1993
			KR 9511739 B1	09-10-1995
			MX 9204021 A1	01-07-1993
			NO 180750 B	03-03-1997

INTERNATIONAL SEARCH REPORT
 information on patent family members

International Application No
PCT/IB 02/00679

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0526004 A		NZ 243472 A	23-12-1993
		PL 170615 B1	31-01-1997
		PL 170893 B1	28-02-1997
		RU 2114113 C1	27-06-1998
		US 5426107 A	20-06-1995
		US 5272147 A	21-12-1993
		ZA 9205084 A	10-01-1994
<hr/>			